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Archives of Internal Medicine

VOLUME 40 DECEMBER, 1927 NUMBER 6

EXPERIMENTS ON WATER AND SALT DIURESIS *

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ROCHESTER, N. Y.

That a typical diuresis follows the ingestion of large amounts of water has been known for some time, but the mechanism by which the water is conveyed from the intestine to the kidneys and the factors stimulating the kidneys to action, whether they are hormone, vascular, nervous, or physicochemical, are not yet proved beyond question. Engel and Scharl,[1] using the refractive index of the serum, Macallum and Benson,[2] using the red blood cell count, Haldane and Priestley,[3] and Adolf,[4] using hemoglobin determinations, found that no dilution of the blood is measurable by these methods when large amounts of water are drunk, although a marked diuresis is produced. Priestley [5] did not find any dilution of the hemoglobin, but a decrease of from 2 to 5 per cent in the conductivity of the serum, indicating a proportionate dilution of the plasma electrolytes. He also found that when an almost isotonic salt solution is drunk the hemoglobin is diluted, the conductivity rises and the diuresis is slight in comparison to that produced by water. In 1921,[6] Priestley carefully determined the water content of the whole blood before and after water was drunk. His method consisted in weighing the samples, drying them over phosphorus pentoxide and reweighing. He found from 2 to 3 per cent more water in the samples taken after 2,000 cc. of water was drunk, but chloride determinations done at the same time showed a 5 or 6 per cent dilution of the total chlorides. He also found that 15 Gm. of sodium chloride produced a diuresis of from 70 to 90 cc. an hour for several hours. Adolf [4] found

* From the laboratories of the Department of Medicine, Johns Hopkins University Medical Department, Baltimore.

1. Engel, Karl; and Scharl, P. J.: Die Konzentrations veränderung des Blutserums nach Wasseraufnahme, Ztschr. f. klin. Med. **60**:225, 1906.

2. Macallum, A. B., and Benson, C. C.: On the Composition of Dilute Renal Excretions, J. Biol. Chem. **6**:87, 1909.

3. Haldane, J. S., and Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **50**:296, 1916.

4. Adolf, E. F.: The Regulation of the Water Content of the Human Organism, J. Physiol. **55**:114, 1921; Chemical Regulation of the Activities of the Human Kidney, Am. J. Physiol. **63**:432, 1923.

5. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **50**:304, 1916.

6. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **55**:305, 1921.

that water taken in excess of that required by the body is promptly excreted; that an isotonic salt solution (sodium chloride) produces a diuresis much less in rate, but lasting much longer than that produced by water; that a hypotonic solution acts as a mixture of isotonic solution and water, the excess water being rapidly excreted, and that a hypertonic solution produces a prolonged diuresis at a rate of from 100 to 200 cc. an hour.

In regard to the stimulus of water and salt diuresis, it appears that the osmotic pressure of the blood [6] is responsible, but as comparatively few experiments have been done and few points determined it was thought well to repeat the work, using more subjects, and taking more frequent blood samples, so as to determine the form of the curve of the dilution of the electrolytes.

METHODS

The subjects for these experiments were healthy white adults, from 20 to 30 years of age, teachers and medical students at the Johns Hopkins Hospital.

In every case, the subject took no food from supper the evening before the experiment was begun until after it was ended. Water was drunk as desired until the beginning of the experiment, after which water was not taken except as noted in the protocols. During the experiments, the subjects worked in the laboratory or on the ward.

Blood was drawn without exposure to air from a vein of the arm either in well fitting Record syringes or in oiled syringes and was immediately injected through capillary glass tubes under oil in heavy walled Pyrex test tubes with a capacity of 10 cc. A one-hole rubber stopper was then inserted and the tube centrifugalized. The serum was removed with pipets with capillary tips. The samples for the refractive index and the determinations of viscosity were drawn in dry syringes and were not put under oil. The blood was drawn under stasis,[7] except in experiments 8 and 9; the stasis, however, was not

7. It has been shown by Dautrebande, Davies and Meakins (The Influence of Circulatory Changes on the Gaseous Exchanges of the Blood, Heart **10**:133, 1923), and more recently by Peters, Bulger, Eiseman and Lee (Total Acid-Base Equilibrium of Plasma in Health and Disease. IV. The Effects of Stasis, Exercise, Hyperpnea, and Anoxemia, and the Causes of Tetany, J. Biol. Chem. **67**:175, 1926) that prolonged venous stasis causes concentration of the peripheral blood, amounting in some cases to 30 per cent. In the experiments of Dautrebande, Davies and Meakins, however, stasis was maintained for twenty-five minutes and more, and "until the forearm and hand had developed a marbled cyanotic appearance and were quite painful" (Peters et al.). In the experiments reported here, the stasis was not maintained in any case for more than two minutes, usually considerably less and in two experiments in which no stasis was used the results were the same as in similar experiments in which stasis had been used. It is therefore felt that the amount of stasis present in these experiments did not appreciably affect the results.

maintained for more than two minutes. No attempt was made to maintain the original carbon dioxide tension of the serum after centrifugalizing; as in preliminary experiments, it was shown that resaturating the serum with alveolar air did not significantly change its conductivity. This has also been shown by Atchley, Loeb, Benedict and Palmer.[8] In preliminary experiments, it was also shown that the conductivity of pig's serum, before and after being put through the same procedure that the blood underwent, did not change by more than 0.04 per cent.

The conductivity was determined by the Wheatstone bridge method, a Kohlrausch bridge and Curtiss coils designed by Leeds and Northrup, and a 500 cycle alternating current from a constant speed generator being used. The apparatus was calibrated against standard resistances from the Department of Physiology. The cell was in the form of a flattened Ostwald pipet containing approximately 1.8 cc. The electrodes, 1 sq. cm. in area and about 0.5 cm. apart, were fixed in the sides of the pipet, from which glass tubes containing mercury made connections with copper wires from the bridge terminals. The lower end of the cell was closed with a clean, one-holed rubber stopper and a glass rod. Constant readings were obtained after washing the cell three times with 0.5 cc. quantities of serum, so that a complete determination could be readily made on 4 cc. of serum. The cell was made to order by Machtlet and Co. of New York and was satisfactory. The cell constant was determined before and after each series of determinations with a fiftieth normal solution of recrystallized potassium chloride in conductivity water. It was found to be approximately 0.327. Three resistances were used in each determination and the results averaged. All determinations were made in a water bath having a constant temperature within a fraction of a degree of 25 C. and corrected to 25 C., a 0.2 per cent increase in conductivity per 0.1 C. rise in temperature being assumed.

The effect of the proteins on the conductivity has not been considered in the calculations, as the determinations of protein were not sufficiently reliable to warrant their use for this purpose, as described below. However, when the effect is appreciable, it will be pointed out in the discussion.

The dilution of the proteins was measured either by the change in the refractive index and viscosity of the serum or by determining the total nitrogen. The refractive index of the serum was determined with an Abbe refractometer, the refractive index of distilled water

8. Atchley, D. W.; Loeb, R. F.; Benedict, Ethel M., and Palmer, W. W.: Physical and Chemical Studies of Human Blood Serum, Arch. Int. Med. **31**:606 (April) 1923.

being taken before each determination. The results are recorded as the refractive index of the solids, being the difference of the refractive indexes of the serum and of distilled water. The viscosity was determined with a Hess viscosimeter. The total nitrogen was determined by

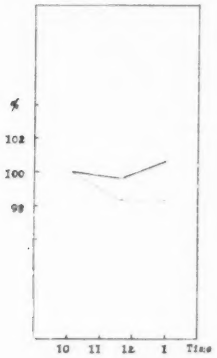

Chart 1

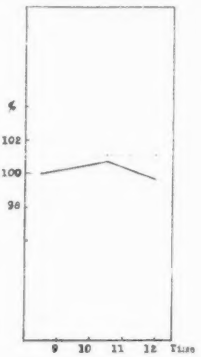

Chart 2

Chart 1 (experiment 1).—Control experiment. In this and in the following charts, the solid line indicates the conductivity of the serum calculated as percentage of first or control sample; the dotted line, refractive index of serum solids or protein by Kjeldahl digestion calculated as percentage of initial sample.

Chart 2 (experiment 2).—Control experiment.

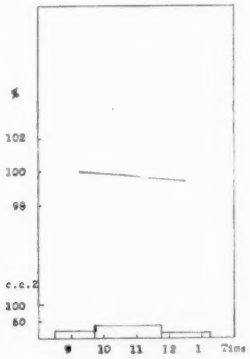

Chart 3 (experiment 3).—Control experiment. In this and in the following charts, the crooked line indicates the rate of secretion of urine in cubic centimeters per hour.

Kjeldahl digestion, 1 cc. of the serum on which the conductivity had been determined being used. The same pipet was used in each case, and duplicate determinations were run in the majority of cases. The results are recorded as percentage of protein, the nonprotein nitrogen being disregarded, as the changes it might undergo would not produce

a significant error. Unfortunately, the determination of the proteins was not accurate enough to be of much value, due to the small amount of serum available. They are given, however, as it is felt that they indicate at least roughly the trend of dilution, and are significant in the experiments with Locke's solution and concentrated salt solution. The probable error amounts to about 5 per cent.

Protocol of Experiment 1

March 30, 1923. No water

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
10:10	Blood.....	0.01195	100	0.0177	100	—	Urine not collected			
11:40	Blood.....	0.01190	99.6	0.0174	98.3	—				
1:00	Blood.....	0.01203	100.6	0.0174	98.3	—				

Protocol of Experiment 2

March 31, 1923. No water

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
8:30	Blood.....	0.01204	100	0.0175	100	1.725	Urine not collected			
10:30	Blood.....	0.01213	100.7	0.0177	101.1	1.775				
12:00	Blood.....	0.01199	99.6	0.0177	101.1	1.750				

Protocol of Experiment 3

June 31, 1923. No water

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
8:30	Bladder emptied									
9:00	Weight, 68,350 Gm.									
9:15	Blood.....	0.012233	100	0.0169	100	1.85				
9:45	Urine.....	.....	.....	.....	.....	.....	27	21.5	1.034	
10:30	Blood.....	0.012204	99.8	0.0169	100	1.84				
11:45	Urine.....	.....	.....	.....	.....	.....	37	37	1.033	
12:30	Blood.....	0.012146	99.4	0.0172	101.8	1.87				
1:15	Urine.....	.....	.....	.....	.....	.....	23	15.5	1.032	
1:30	Weight, 67,650 Gm.									

Urine was collected as noted in the protocols, and the volume measured with an accuracy of 2 per cent. Either the specific gravity or the conductivity or both was determined, an ordinary hygrometer and the conductivity apparatus described above being used.

EXPERIMENTS

Experiments 1, 2 and 3 (figs. 1, 2 and 3) were run as controls, no water being taken. The irregular variation of the conductivity, amounting to 1.1 per cent in experiment 2, is possibly due to the frequent changes in blood flow and metabolism that are bound to occur in the arm of an individual who is moving about at work.

Six experiments (figs. 4, 5, 6, 7, 8 and 9) were done in which water was taken. The curve of the diuresis is similar in all, an abrupt rise to a peak in from one to two hours, and a more gradual decline. In experiment 6, the decrease in conductivity parallels the rate of diuresis, but in the other experiments (except experiment 7), there is a tendency for the diuresis to lag from one-half to one hour behind the drop in conductivity. The greatest change in conductivity noted is 3.8 per cent in experiment 5.

As stated, the protein curves are too irregular to warrant any conclusions, except that in only one case, experiment 7, is there any definite dilution.

In experiment 7, a small volume of distilled water was taken, producing a definite diuresis, which is contrary to what Hashimoto [9]

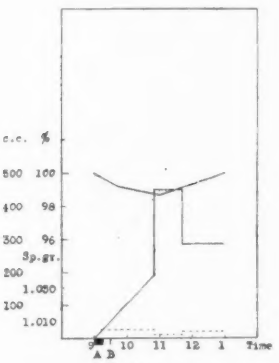

Chart 4

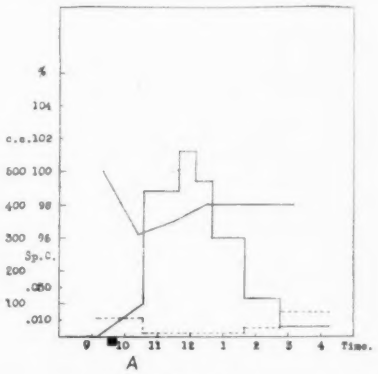

Chart 5

Chart 4 (experiment 4).—Water drinking experiment.

Chart 5 (experiment 5).—Water drinking experiment. At *A*, 2 liters of tap water was given by mouth.

found to be the case with dogs. Unfortunately, in this experiment the greatest depression of the conductivity curve was missed, the second sample of blood being taken after the return to normal had begun. At the end of the experiment, a fifth sample of blood was drawn six minutes after the fourth sample, stasis having been maintained meanwhile. The results show a drop in conductivity and an increase in protein, which is in accord with Dautrebande, Davies and Meakins,[7] and is what one would expect from Henderson's [10] nomogram, with a rise of carbon dioxide in the tissues.

9. Hashimoto, M.: Zur Frage der aus dem Verdaungstrakt darstelbaren diuretisch virkenden Substanz, Arch. f. exper. Path. u. Pharm. **76**:367, 1914.

10. Henderson, L. J.; Bock, A. V.; Field, H., and Stoddart, J. L.: Blood as a Physicochemical System, J. Biol. Chem. **59**:379, 1924.

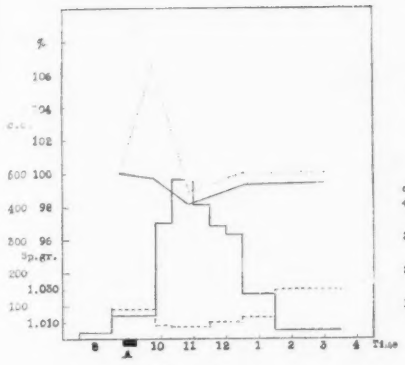

Chart 6

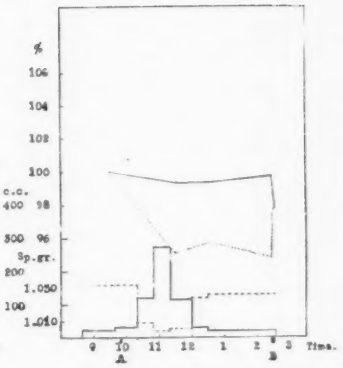

Chart 7

Chart 6 (experiment 6).—Water drinking experiment. At *A*, 2 liters of tap water was given by mouth.

Chart 7 (experiment 7).—Water drinking experiment. At *A*, 700 cc. of distilled water was given by mouth. At *B*, stasis was maintained for six minutes between the fourth and fifth samples of blood.

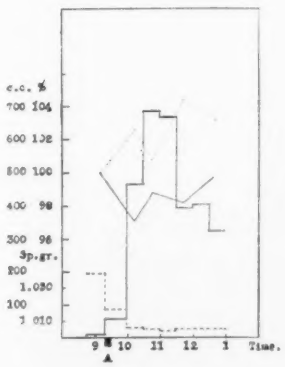

Chart 8

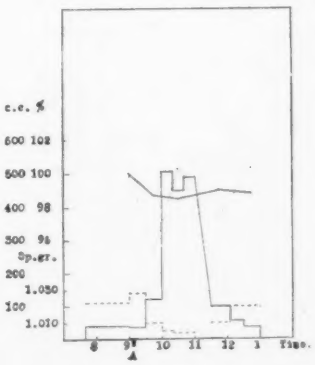

Chart 9

Chart 8 (experiment 8).—Water drinking experiment. At *A*, 1,400 cc. of tap water was given by mouth.

Chart 9 (experiment 9).—Water drinking experiment. At *A*, 1 liter of tap water was given by mouth.

Protocol of Experiment 4

March 31, 1923

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
9:00	Blood	0.01198	100	0.0176	100	1.75				
9:01-9:15	2,000 cc. tap water by mouth									
9:30	1,000 cc. vomited									
9:45	Blood	0.01188	99.2	0.0169	96.1	1.75				
10:50	Urine	.....	.....	.....	.....	.....	360	....	1.005	
11:00	Blood	0.01181	98.7	0.0174	98.9	1.75				
11:40	Urine	.....	.....	.....	.....	.....	390	....	1.002	
12:55	Urine	.....	.....	.....	.....	.....	345	....	1.004	
1:00	Blood	0.01197	100	0.0174	98.9	1.75				

Protocol of Experiment 5

April 2, 1923

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
9:10	Bladder emptied									
9:20	Blood	0.01221	100	0.0167	100	1.73				
9:30-9:45, 2,000 cc. of tap water by mouth										
10:25	Blood	0.01174	96.2	0.0176	105.3	1.73				
10:35	Urine	.....	.....	.....	.....	.....	140	99	.....	0.01139
11:30	Blood	0.01184	97.0	0.0167	100	1.72				
11:40	Urine	.....	.....	.....	.....	.....	475	439	.....	0.00274
12:10	Urine	.....	.....	.....	.....	.....	280	560	.....	0.00233
12:30	Blood	0.01196	98.0	0.0168	100.6	1.72				
12:40	Urine	.....	.....	.....	.....	.....	235	470	.....	0.00231
1:40	Urnie	.....	.....	.....	.....	.....	300	300	.....	0.00235
2:45	Urine	.....	.....	.....	.....	.....	125	115	.....	0.00522
3:10	Blood	0.01196	98.0	0.0172	103	1.72				
4:15	Urine	.....	.....	.....	.....	.....	46	30	.....	0.01518

Protocol of Experiment 6

June 5, 1923

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
7:30	Bladder emptied									
8:35	Weight, 68,100 Gm.									
8:30	Urine	.....	.....	.....	.....	....	20	20	?	0.026
8:45	Blood	0.012109	100	0.0169	100	1.86				
8:50-9:15, 2,000 tap water by mouth										
9:45	Blood	0.012073	99.7	0.0180	106.5	2.00				
9:50	Urine	.....	.....	.....	.....	....	94	70.5	1.018	0.011
10:20	Urine	.....	.....	.....	.....	....	175	350	1.008	0.002
10:50	Blood	0.011869	98.1	0.0167	98.9	1.82				
11:00	Urine	.....	.....	.....	.....	....	320	480	1.007	0.002
11:30	Urine	.....	.....	.....	.....	....	202	404	1.007	0.002
12:00	Urine	.....	.....	.....	.....	....	170	340	1.010	0.002
12:30	Urine	.....	.....	.....	.....	....	158	316	1.010	0.002
12:32	Blood	0.012017	99.3	0.0169	100	1.87				
1:30	Urine	.....	.....	.....	.....	....	135	135	1.013	0.004
3:00	Blood	0.012035	99.4	0.0169	100	1.87				
3:30	Urine	.....	.....	.....	.....	....	48	24	1.030	0.019
3:35	Weight, 67,870 Gm.									

Protocol of Experiment 7

November 4, 1923

Time	Notes	Blood: Specific Conductivity	Blood: Per Cent	Blood: Refractive Index	Blood: Per Cent	Blood: Protein	Blood: Per Cent	Urine: Amount	Urine: Rate	Urine: Specific Gravity
8:40	Bladder emptied									
9:30	Blood	0.01186	100	0.0204	100	8.21	100			
9:40	Urine	.....	.....	.....	.....	....	.....	22	22	1.032
9:41	Weight, 67,000 Gm.									
9:50	700 cc. distilled water by mouth									
10:20	Urine	.....	.....	.....	.....	....	.....	15	30	1.032
10:30	Blood	0.01178	99.3	0.0211	103.4	7.81	95.1			
10:50	Urine	.....	.....	.....	.....	....	.....	60	120	1.009
11:20	Urine	.....	.....	.....	.....	....	.....	136	272	1.004
11:32	Blood	0.01178	99.3	0.0193	94.6	7.86	95.7			
12:00	Urine	.....	.....	.....	.....	....	.....	77	115	1.005
12:30	Urine	.....	.....	.....	.....	....	.....	15	30	1.024
2:25	Blood	0.01181	99.7	0.0173	84.8	7.78	94.8			
2:31	Blood, after stasis	0.01159	97.8	0.0182	89.2	8.57	104.3	40	19.2	1.026
2:35	Urine	.....	.....	.....	.....	....	.....			
2:40	Weight, 67,000 Gm.									

Protocol of Experiment 8

June 3, 1924

Time	Notes	Blood: Specific Conductivity	Blood: Per Cent	Blood: Protein	Blood: Per Cent	Urine: Amount	Urine: Rate	Urine: Specific Gravity
8:46	Bladder emptied							
9:10	Blood	0.01186	100	7.12	100			
9:17	Urine	.....	.....	....	.....	9	8.5	1.039
9:17–9:27, 1,400 cc. tap water by mouth								
9:57	Urine	.....	.....	....	.....	38	57	1.017
10:12	Blood	0.01151	97.1	7.31	102.6			
10:27	Urine	.....	.....	....	.....	232	464	1.006
10:43	Blood	0.01172	98.8	7.18	100.8			
10:57	Urine	.....	.....	....	.....	342	684	1.005
11:27	Urine	.....	.....	....	.....	334	668	1.004
11:42	Blood	0.01165	98.2	7.44	104.4			
11:57	Urine	.....	.....	....	.....	197	394	1.005
12:27	Urine	.....	.....	....	.....	202	404	1.005
12:42	Blood	0.01184	99.8	7.35	103.2			
12:57	Urine	.....	.....	....	.....	162	324	1.005

Protocol of Experiment 9

June 7, 1924

Time	Notes	Blood: Specific Conductivity	Blood: Per Cent	Blood: Protein	Blood: Per Cent	Urine: Amount	Urine: Rate	Urine: Specific Gravity
7:40	Bladder emptied							
9:00	Blood	0.01183	100	7.23	100			
9:02	Urine	.....	.....	....	.....	54	39.5	1.022
9:05–9:10, 1,000 cc. tap water by mouth								
9:30	Urine	.....	.....	....	.....	17	36.5	1.028
9:45	Blood	0.01167	98.7	6.90	95.4			
10:00	Urine	.....	.....	....	.....	61	122	1.010
10:20	Urine	.....	.....	....	.....	168	504	1.005
10:30	Blood	0.01165	98.5	7.26	100.3			
10:41	Urine	.....	.....	....	.....	157	449	1.004
11:01	Urine	.....	.....	....	.....	163	489	1.004
11:31	Urine	.....	.....	....	.....	—	—	—
11:46	Blood	0.01171	99.0	7.05	97.5			
12:05	Urine	.....	.....	....	.....	56	99	1.010
12:30	Urine	.....	.....	....	.....	23	55	1.020
12:45	Blood	0.01169	98.8	7.26	100.3			
1:00	Urine	.....	.....	....	.....	19	38	1.020

Two experiments (figs. 10 and 11) were done in which Locke's solution was taken. The diuresis is similar to a water diuresis, in that there is a sharp rise and fall, but it is much less in amount, and excretion continues for some hours at a rate slightly above normal. The rise in conductivity of the serum may be partly explained by the dilution of the proteins.

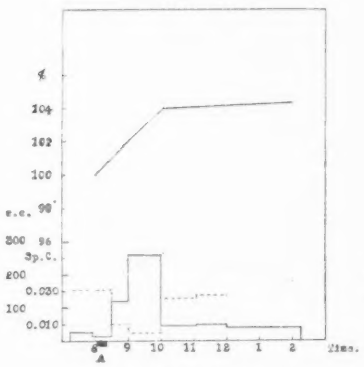

Chart 10

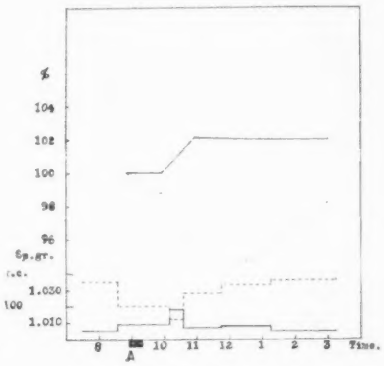

Chart 11

Chart 10 (experiment 10).—Locke's solution experiment. At *A*, 2 liters of Locke's solution was given by mouth.

Chart 11 (experiment 11).—Locke's solution experiment. At *A*, 2 liters of Locke's solution was given by mouth. Specific conductivity of solution 0.0135.

Protocol of Experiment 10

April 4, 1923

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
7:15	Bladder emptied									
7:53	Urine.....	.....	.....	.....	.....	....	17	27	—	0.030
8:00	Blood.....	0.01176	100	0.0170	100	1.77				
8:05–8:20, 2,000 cc. Locke's solution by mouth										
8:30	Urine.....	.....	.....	.....	.....	....	10	16	—	0.030
8:50	Blood.....	0.01197	101.7	0.0160	94.2	1.70				
9:00	Urine.....	.....	.....	.....	.....	....	60	120	—	0.010
10:00	Urine.....	.....	.....	.....	.....	....	260	260	—	0.005
10:05	Blood.....	0.01214	104.0	0.0162	95.3	1.71				
11:05	Urine.....	.....	.....	.....	.....	....	50	46	—	0.026
12:00	Urine.....	.....	.....	.....	.....	....	45	49	—	0.028
2:00	Blood.....	0.01226	104.3	0.0159	93.6	1.70				
2:15	Urine.....	.....	.....	.....	.....	....	90	40	—	—

Protocol of Experiment 11

June 5, 1923

Time	Notes	Blood: Specific Conductivity	Blood: Per Cent	Blood: Refractive Index	Blood: Per Cent	Blood: Viscosity	Urine: Amount	Urine: Rate	Urine: Specific Gravity
7:30	Bladder emptied								
8:35	Urine	.....	.....	.....	.....	....	28	28	1.035
8:40	Weight, 67,750 Gm.								
8:50	Blood	0.012179	100	0.0170	100	1.92			
8:55-9:20, 2,000 cc. Locke's solution by mouth*									
9:55	Blood	0.012179	100	0.0168	98.8	1.86			
10:10	Urine	.....	.....	.....	.....	....	72	45.5	1.020
10:35	Urine	.....	.....	.....	.....	....	37	89	1.012
10:55	Blood	0.012428	102.1	0.0161	94.7	1.83			
11:45	Urine	.....	.....	.....	.....	....	38	32.5	1.028
12:30	Blood	0.012122	102	0.0161	94.7	1.81			
1:15	Urine	.....	.....	.....	.....	....	56	37.5	1.033
3:00	Blood	0.012422	102	0.0167	98.2	1.82			
3:15	Urine	.....	.....	.....	.....	....	53	26.5	1.036
3:16	Weight, 68,250 Gm.								

* Specific conductivity of Locke's solution, 0.01325 at 25 C.

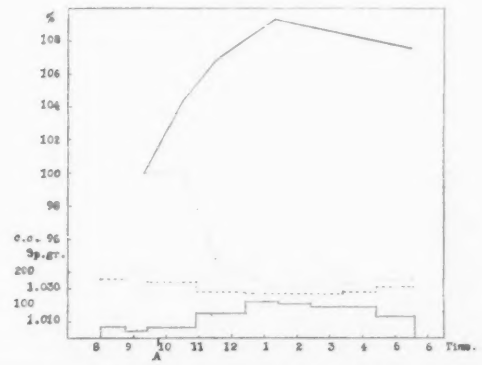

Chart 12 (experiment 12).—Hypertonic salt solution experiment. At *A*, 500 cc. of salt solution was given by mouth. The solution was composed of 7 per cent sodium chloride; 0.3 per cent potassium chloride; 0.25 per cent calcium chloride; trace, sodium bicarbonate.

In one experiment (fig. 12), 500 cc. of a salt solution of the same composition as Locke's solution, but ten times as concentrated, was taken. There was a 9.3 per cent increase in the conductivity, which is only partly explained by the dilution of the proteins. The hydremia is probably due to the influx of water from the tissues following the increase in the osmotic pressure of the plasma.

Priestley [6] found that the injection of solution of pituitary following the drinking of water delayed the diuresis for five or six hours,

Protocol of Experiment 12

June 9, 1923

		Blood					Urine			
Time	Notes	Specific Conductivity	Per Cent	Refractive Index	Per Cent	Viscosity	Amt.	Rate	Specific Gravity	Specific Conductivity
8:00	Bladder emptied									
8:45	Urine	.....	.....	.....	.....	.....	25	33.5	1.036	0.038
8:50	Weight, 68,325 Gm.									
9:20	Blood	0.012131	100	0.0172	100	1.82				
9:25	Urine	.....	.....	.....	.....	.....	15	22.5	?	0.039
9:30-9:45, 500 cc. salt solution by mouth*										
10:30	Blood	0.012659	104.3	0.0172	100	1.81				
10:55	Urine	.....	.....	.....	.....	.....	50	33.5	1.034	0.040
11:30	Blood	0.012956	106.8	0.0163	94.8	1.79				
12:25	Urine	.....	.....	.....	.....	.....	105	73.5	1.028	0.039
1:20	Blood	0.013258	109.3	0.0160	93.0	1.77				
1:25	Urine	.....	.....	.....	.....	.....	110	110	1.027	0.038
2:25	Urine	.....	.....	.....	.....	.....	105	105	1.027	0.041
3:25	Urine	.....	.....	.....	.....	.....	95	95	1.027	
4:25	Urine	.....	.....	.....	.....	.....	95	95	1.028	0.042
5:30	Blood	0.013056	107.6	0.0161	93.6	1.77				
5:35	Urine	.....	.....	.....	.....	.....	75	64.5	1.031	0.043
5:40	Weight, 67,850 Gm.									

* The solution was composed of 7 per cent sodium chloride; 0.3 per cent potassium chloride; 0.25 per cent calcium chloride; trace, sodium bicarbonate.

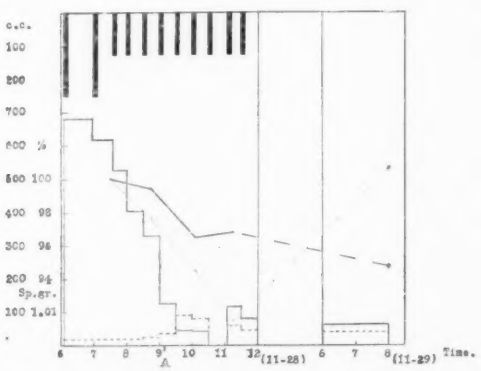

Chart 13 (experiment 13).—Experiment with solution of pituitary in diabetes insipidus. The heavy black areas at the top of the chart indicate cubic centimeters of water by mouth. At *A*, 0.6 cc. of solution of pituitary was given subcutaneously.

but that when it did occur it was normal in amount and rate. Weir [11] reviewed the literature on the study of changes in the blood and urine in cases of diabetes insipidus in which solution of pituitary was given, and reported three cases of his own. The prevailing opinion is that the solution of pituitary acts on the kidney cells, causing a retention of water. Experiment 13 (fig. 13) was done on a white boy, aged 17,

11. Weir, J. F.: Pituitary in Diabetes Insipidus, Arch. Int. Med. **32**:617 (Oct.) 1923.

who three weeks previously had received a cranial injury in an automobile accident. Following the accident he was unconscious for three days, and twenty-four hours after regaining consciousness he began to complain of great thirst. Since that time, he has had diabetes insipidus with a urine output of from 5 to 10 liters a day. At the time of the experiment, he was on a salt-free diet, which explains the failure of the conductivity of the blood to return to normal on the following day. The dilution of both the electrolytes and the blood proteins would indicate that there was a definite water retention due to a specific action of solution of pituitary on the kidney cells.

*Protocol of Experiment 13**

Nov. 28, 1923		Blood				Urine		
Time	Notes	Specific Conductivity	Per Cent	Protein	Per Cent	Amount	Rate	Specific Gravity
6:05	Bladder emptied, 250 cc. water							
6:57	Urine	.....	.....	....	.....	590	681	1.004
6:58	250 cc. water							
7:30	Blood	0.01218	100	8.80	100			
7:34	Urine	.....	.....	....	.....	382	619	1.004
7:35	125 cc. water							
8:00	125 cc. water. Urine	.....	.....	....	.....	228	526	1.004
8:30	125 cc. water. Urine	.....	.....	....	.....	202	404	1.004
8:45	Blood	0.01210	99.4	8.59	97.6			
9:00	125 cc. water Urine	.....	.....	....	.....	165	330	1.005
9:10	0.6 cc. solution of pituitary							
9:30	125 cc. water. Urine	.....	.....	....	.....	62	124	1.007
10:00	125 cc. water. Urine	.....	.....	....	.....	22	44	1.018
10:05	Blood	0.01175	96.5	8.32	94.5			
10:30	125 cc. water. Urine	.....	.....	....	.....	21	42	1.016
11:05	125 cc. water. Urine	.....	.....	....	.....	0		
11:15	Blood	0.01179	96.8	7.97	91.5			
11:30	125 cc. water. Urine	.....	.....	....	.....	48	115	1.012
12:00	Urine	.....	.....	....	.....	39	78	1.009
Nov. 29, 1923								
6:00	Bladder emptied							
8:00	Blood and urine	0.01153	94.7	8.86	100.6	120	60	1.008

* This patient had diabetes insipidus, following a traumatic injury to the head. He was on a salt-free diet, less than 0.5 Gm. of salt a day.

RESULTS

The results of the experiments described are in accord with the theory that the osmotic pressure of the plasma is the stimulus of water and salt diuresis. The inaccuracy of the protein determinations is unfortunate, but does not affect the argument, as previous workers have clearly established, that hydremia is absent or is only slight during water diuresis. Priestly found a 2 or 3 per cent increase in water, and there is no reason to suppose that a genuine hydremia may not occur in some cases. The lag of the diuresis following the drop in conductivity shown in some of these experiments is important as indicating that there is probably another factor as well as the osmotic pressure of the plasma concerned with the initiation of a water diuresis. In order to determine this more accurately, more frequent samples of blood should be taken

than is expedient with the human subject. Also arterial, rather than venous, blood should be used, as small changes in the concentration of the electrolytes are significant. For this reason, large dogs were used as subjects in further experiments. The results, to be published shortly, confirm the observation of a lag in the diuresis after the drop in conductivity of the serum.

SUMMARY

In three control experiments on two subjects, the conductivity of blood from the basilic vein varied from 0.6 to 1.1 per cent during the morning when no food or water was taken.

In six experiments on four subjects, from 700 to 2,000 cc. of water was taken by mouth. The conductivity of the blood serum dropped rapidly and rose more slowly. The greatest drop was 3.8 per cent. The diuresis either paralleled the variation of the conductivity or lagged thirty or forty-five minutes behind it. Protein determinations on the blood were unsatisfactory, but in only one case indicated any definite dilution.

In two experiments on one subject, 2,000 cc. of Locke's solution was taken. The conductivity increased by 4.3 per cent and 2.1 per cent. The diuresis amounted to 260 cc. an hour in one case but only to 45 cc. an hour in the other. The dilution of the proteins was fairly definite.

In one experiment, 500 cc. of salt solution ten times the concentration of Locke's solution was taken. The conductivity went up nearly 10 per cent. The diuresis did not exceed 110 cc. an hour, but was prolonged.

In one experiment in a case of diabetes insipidus following the subcutaneous injection of 0.6 cc. of solution of pituitary the conductivity dropped, the proteins were diluted and the diuresis checked, with anuria for one period of thirty minutes.

CHANGES IN THE EYEGROUND IN VASCULAR DISEASES AND IN RELATED CONDITIONS

ONE HUNDRED AND EIGHTY-SEVEN HYPERTHYROID, DIABETIC, NEPHRITIC, HYPERTENSIVE AND CARDIAC CASES, WITH SPECIAL REFERENCE TO RETINAL ARTERIOSCLEROSIS *

HUGO O. ALTNOW, M.D.
MINNEAPOLIS

Contributions to the literature on the study of the eyeground have been numerous, but the majority have been made by ophthalmologists or by internists in collaboration with ophthalmologists. While engaged in the study of vascular diseases at the Peter Bent Brigham Hospital, from February, 1924, to July, 1925, I had an unusual opportunity to study eyegrounds in various vascular diseases and related conditions. Because of the importance that retinal vascular changes have assumed in the diagnosis and interpretation of general vascular disease, I feel that it will be of interest to internists, ophthalmologists and practitioners of medicine to get the point of view of an internist who has had the opportunity to examine a large group of fundi in various diseases. This is a study of eyeground changes and the manner in which they indicate, or reflect, general disorders from the standpoint of one interested chiefly in the problems of internal medicine.

All patients who were admitted consecutively to the medical wards of the Peter Bent Brigham Hospital for an eight months' period (Aug. 1, 1924, to April 1, 1925) with diagnoses of exophthalmic goiter, toxic adenoma of the thyroid, diabetes, acute and subacute nephritis, chronic nephritis, vascular hypertension, chronic myocarditis with and without arrhythmia, cardiac infarction, angina pectoris or chronic cardiac valvular disease were subjected to a thorough study of the eyeground. The ophthalmoscopic examination was made with the pupils dilated, at the same time that blood pressure readings were made, and after the patient had been in bed for several days. The blood pressure readings, therefore, probably represent basal blood pressures. Cases in which diagnoses were doubtful when the patients were discharged from the hospital are not included in this report. The original purpose of this study was to obtain a record of changes in the eyeground in certain groups of vascular and related conditions. In addition, some comments will be made on the clinical aspects of the changes.

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* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

In determining the presence of retinal arteriosclerosis, I have adopted as primary evidence of its existence the criteria of O'Hare and Walker.[1] I quote their statement:

> The two signs of arteriosclerosis (retinal) that are absolute and beyond criticism . . . are compression effects at the arteriovenous crossings and irregularity of the lumen (of the arteries).

They feel that the other less important signs are too variable and depend too much on personal judgment to be infallible. As secondary evidence of retinal arteriosclerosis, I have accepted, in the order of their importance, the following: (1) lack of uniformity in the light streak, particularly when dulled in segments and bright in others; (2) narrowing of the central light streak, especially in branches of the second and third order; (3) loss of translucency (early copper wire artery); (4) narrowing of the whole vessel and (5) tortuosity of two types: the corkscrew tortuosity of the macular artery and the "wide-looped" tortuosity of the larger vessels. The first four changes are included under departures from the normal in the normal arterial reflex. The wide-looped tortuosity is probably due to loss of elasticity and rigidity of the main temporal and nasal arteries. These changes are considered by Moore[2] as indicating retinal arteriosclerosis. Typical copper wire arteries, obliteration, beading and calcification take their place together with irregularity of the lumen and arteriovenous compression, as undeniable evidence of retinal arteriosclerosis.

In the interpretation and comments on the relation of sclerosis of the retinal vessels to vascular hypertension, I am accepting as my criterion the work of O'Hare and Walker[1] and their observations on sixteen patients with normal or low blood pressures who previously were known to have had hypertension. Fourteen patients in this group had definite retinal arteriosclerosis. O'Hare and Walker believe that the recurrence of retinal arteriosclerosis indicates the probability of a previous hypertension. From my own observations in examining similar cases, I am strongly inclined to verify their opinion. This is also in accord with the view held by Fahr,[3] who says that so far as his investigations go, definite irregularities of the lumen and arteriovenous compressions are indications of a previous hypertension, even though at the time of examination the blood pressure is within normal limits.

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1. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924.

2. Moore, R. F.: Retinitis of Arteriosclerosis and Relation to Renal Retinitis and to Cerebral Vascular Disease, Quart. J. Med. **10**:29 (Oct.-Jan.) 1916-1917.

3. Fahr, G. E.: Personal communication to author.

The ophthalmoscopic appearance and the changes in the vessels due to sclerosis of the retinal arteries will receive special consideration when I comment on the changes in the cardiac group. In this group the majority of cases showed definitely recognizable vascular changes, usually unaccompanied by any marked retinal edema or retinitis. This made detailed study of these changes possible. However, there is no essential difference in the vascular changes described in this group as compared to those observed in the cases in the other groups in which retinal vascular sclerosis was present.

GROUP I: CHANGES IN THE EYEGROUND IN EXOPHTHALMIC GOITER AND IN TOXIC ADENOMA OF THE THYROID

In the selection of the cases included in table 1, namely, those of exophthalmic goiter and adenoma of the thyroid, only patients with elevated basal metabolic rates were included. As the increased metabolism demands an increased cardiac output, and since increased cardiac output is one factor in producing hypertension and another is increased resistance in the vascular periphery, it seemed desirable to study the retinal vessels in a group of these cases. In exophthalmic goiter, increased cardiac output produces only moderate elevation of the systolic blood pressure, if the pressure is increased at all. The increased cardiac output produces increased pulse pressure, largely by lowering the diastolic blood pressure if the vascular periphery is normal. There can be little doubt that the arterial system undergoes some strain in this adaptation. In toxic adenoma (probably because of the factor of increased age), the diastolic pressure is more likely to be at a fixed level, and in order that the circulation may adapt itself to the increased cardiac output, an elevation in the systolic blood pressure must take place. The increased cardiac output is the result of increased cardiac rate.

The incidence of retinal arteriosclerosis in this group will be commented on with reference to the absence or presence of hypertension,[4] and not on the basis of the clinical diagnosis, since the diagnosis was not always definite on whether the case was one of exophthalmic goiter or of toxic adenoma. However, out of eleven cases in which the condition was diagnosed as exophthalmic goiter, only four (128, 134, 136 and 139) showed definite retinal arteriosclerosis. In these four, three

4. In this, as well as in the other groups studied, a systolic blood pressure of 145 mm. has been arbitrarily chosen as the dividing line between nonhypertensive and hypertensive cases. Patients with a systolic blood pressure within a range of from 145 to 160 are considered to have slight hypertension, while a range of from 160 to 180 indicates moderate hypertension and above 180 marked hypertension. I am aware that many clinicians will consider from 145 to 160 mm. a low range to come within the definition of hypertension.

TABLE 1.—*Changes in the Eyeground in Patients with Exophthalmic Goiter and Adenoma of the Thyroid*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
121	Hyperthyroidism	27	102/68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
122	Hyperthyroidism	24	112/74	0	0	0	0	0	0	0	++	0	0	0	0	0	0	No retinal arteriosclerosis
123	Exophthalmic goiter with hyperthyroidism	29	116/72	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
124	Exophthalmic goiter with hyperthyroidism	22	118/58	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
125	Chronic myocarditis, hyperthyroidism	34	128/53	0	0	0	0	0	0	0	0	±	++	0	0	±	0	Doubtful retinal arteriosclerosis
126	Chronic myocarditis, auricular fibrillation, hyperthyroidism	46	132/80	0	0	0	0	0	0	+	++	0	++	0	0	±	0	Doubtful retinal arteriosclerosis
127	Exophthalmic goiter, hyperthyroidism	15	134/68	0	0	0	0	0	0	0	0	0	+	0	0	0	0	Doubtful retinal arteriosclerosis
128	Exophthalmic goiter, myocarditis	54	134/68	0	0	0	0	0	0	0	0	++	+++	+	0	++	+	Definite retinal arteriosclerosis
129	Exophthalmic goiter, hyperthyroidism	31	138/74	0	0	0	0	0	0	+	+	0	++	0	0	0	0	No retinal arteriosclerosis
130	Exophthalmic goiter, hyperthyroidism	48	138/82	0	0	0	0	0	0	0	0	0	++	0	0	±	++	Doubtful retinal arteriosclerosis
131	Exophthalmic goiter, auricular fibrillation	46	140/70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
132	Exophthalmic goiter, hyperthyroidism	39	142/76	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
133	Exophthalmic goiter, hyperthyroidism	58	146/0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
134	Exophthalmic goiter, chronic myocarditis, auricular fibrillation	35	148/60	0	+	0	0	0	0	0	0	0	++	0	0	++	0	Definite retinal arteriosclerosis
135	Exophthalmic goiter, hyperthyroidism	48	152/72	0	0	0	0	0	0	0	0	0	+++	0	0	+	0	Definite retinal arteriosclerosis
136	Exophthalmic goiter, hyperthyroidism, hypertension	52	162/84	0	0	0	0	0	0	0	+++	++	+++	0	+	++	0	Definite rertinal arteriosclerosis
137	Adenoma of thyroid, hyperthyroidism	52	168/62	+	+	0	0	0	0	0	0	+	+	0	0	+	++	Definite retinal arteriosclerosis
138	Thyroid adenoma, chronic myocarditis	61	168/100	0	0	0	0	0	0	0	++	+	++	0	0	++	0	Definite retinal arteriosclerosis
139	Exophthalmic goiter, chronic myocarditis, auricular fibrillation	59	184/76	0	0	0	0	0	0	0	+	0	++	0	0	++	0	Definite retinal arteriosclerosis
140	Thyroid adenoma, hyperthyroidism, myocarditis and auricular fibrillation	62	242/130	0	0	0	0	0	++	+	++	++	++	0	0	++	++	Definite retinal arteriosclerosis, grayish white and buff spots, early chorioretinitis

of the patients (128, 136 and 139) were of an age at which the vascular degenerative processes begin to manifest themselves. Three patients (137, 138 and 140) with a condition diagnosed as toxic adenoma showed definite retinal arteriosclerosis. They also fell into the same age group. The incidence of retinal arteriosclerosis in the nonhypertensive and hypertensive patients is shown in table 2.

SUMMARY OF GROUP I

When this group is viewed as a whole and the cases in the sixth decade and older are eliminated, one sees a rather striking absence of retinal arteriosclerosis. This lends support to the idea, expressed later, that retinal arteriosclerosis is secondary to hypertension. This is, to some extent, in accord with the observations of Benedict,[5] who states:

> Cardiac stimulation alone is insufficient to produce vascular sclerosis, even with the presence of long-continued high blood pressure, is the conclusion reached after the study of exophthalmic goiter.

TABLE 2.—*Retinal Arteriosclerosis in Group I*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	8.3	25.0	66.7
With hypertension	87.5	0.0	12.5

GROUP II: CHANGES IN THE EYEGROUND IN DIABETES

The changes in the eyegrounds of forty-seven diabetic patients of all ages (children under 12 years excluded) are included in table 3. The frequency of the occurrence of retinal arteriosclerosis is shown in table 4.

SUMMARY OF GROUP II

In the nonhypertensive and hypertensive groups together, the incidence of retinal arteriosclerosis was 42.5 per cent. According to the criteria adopted in the interpretations in this study, it would mean that this many patients probably had hypertension prior to, or during, the diabetes. O'Hare and Walker [6] suggest that hypertension may play an important part in the etiology of diabetes in elderly persons, and that hypertension, instead of terminating in cerebral arteriosclerosis, cardiac failure or chronic nephritis, may terminate in diabetes. O'Hare,[7] in a study of the dextrose tolerance of patients with hypertension, has

5. Benedict, W. L.: Retinitis of Hypertension, American Medicine, new series, **17**:467 (June) 1923.

6. O'Hare, J. P., and Walker, W. G.: Heart in Hypertension, Boston M. & S. J. **190**:683 (April 24) 1924.

7. O'Hare, J. P.: Glucose Tolerance Test in Chronic Vascular Hypertension, Am. J. M. Sc. **160**:966, 1920.

TABLE 3.—*Changes in Eyeground in Forty-Seven Patients with Diabetes*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
141	Diabetes 6 months	26	80/52	0	0	0	0	0	0	+	0	0	0	0	0	0	+	No retinal arteriosclerosis
142	Diabetes 7 months	35	90/52	0	0	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis
143	Diabetes 3 years	13	98/65	±	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, retinas red
144	Diabetes 1 month	40	98/60	0	0	0	0	0	0	0	0	0	++	0	+	0	+	No retinal arteriosclerosis
145	Diabetes, secondary anemia 1½ years	13	98/52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
146	Diabetes 3 years	14	98/64	0	0	0	0	0	0	0	++	0	0	0	0	0	0	No retinal arteriosclerosis
147	Diabetes 5 years	36	102/60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, nonmedullated nerve fibers
148	Acidosis, diabetes 1 year	17	102/58	0	0	0	0	0	0	0	0	0	++	0	0	0	0	No retinal arteriosclerosis
149	Diabetes 4½ years	47	104/76	0	0	0	0	0	0	0	0	±	++	0	0	±	0	Doubtful retinal arteriosclerosis
150	Diabetes, pulmonary tuberculosis 3 years	20	106/56	0	0	0	0	0	0	+	+	0	0	0	0	0	0	No retinal arteriosclerosis
151	Diabetes, arteriosclerosis 3 months	46	106/76	0	0	0	0	0	0	+	0	0	+	0	0	0	+	No retinal arteriosclerosis
152	Diabetes 4 years	33	106/52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, retinas red
153	Diabetes 2 years	20	108/81	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
154	Diabetes, arteriosclerosis 8 to 10 years	60	112/86	0	Pallor	0	0	0	0	0	0	+++	0	0	0	0	++ ++	Definite retinal arteriosclerosis, advanced chorioretinitis, contracted vessels
155	Diabetes 1 year	26	114/66	0	0	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis
156	Diabetes 3 years	31	114/72	0	0	0	0	0	0	0	0	0	+	0	0	0	+	No retinal arteriosclerosis
157	Diabetes, arteriosclerosis 5 years	71	116/78	++	0	0	0	+	++++	0	+++	+++	+++	0	++	+++	+++	Definite retinal arteriosclerosis, old papilledema, with secondary optic atrophy, superficial hemorrhages, numerous grayish white spots, sheathing of vessels
158	Diabetes with coma, pulmonary tuberculosis 2 years	42	122/76	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis

159	Diabetes, syphilis diabetic catract 4 years	50	122/76	0	0	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis, beginning cataract in the left eye
160	Diabetes 6 months	52	124/70	See note	0	0	0	0	0	0	0	0	0	0	0	±	++	Doubtful retinal arteriosclerosis, conus temporalis, edge of disk has "fuzzy" appearance
161	Diabetes, myocarditis, adhesive pericarditis ?	54	126/68	±	0	0	0	+	0	0	0	++	+	0	+	0	++	Definite retinal arteriosclerosis, small round hemorrhages
162	Diabetes, hypertension 1 year	47	128/84	0	0	0	0	0	0	0	+++	+	+++	0	0	++	+	Definite retinal arteriosclerosis, rejected 1 year ago for insurance on account of hypertension
163	Diabetes, hypertension ?	62	128/76	0	0	0	0	+++	+++	0	0	0	0	0	0	++	⊕	Definite retinal arteriosclerosis small round and large superficial hemorrhages, finely pencled macular fan, "diabetic retinitis"
164	Diabetes 3 months	50	128/74	0	0	0	0	+	++	0	++	0	++	0	++	+	0	Doubtful retinal arteriosclerosis, small round hemorrhages, buff and small white spots
165	Diabetes, tumor of the brain ?	52	130/85	+	0	0	0	0	0	0	++	±	++	+	0	++	0	Definite retinal arteriosclerosis
166	Diabetes 4 to 5 years	46	132/78	0	0	0	0	++	0	0	++ ++	+	++	+	++	++ ++	+	Definite retinal arteriosclerosis, small, round hemorrhages
167	Diabetes, primary anemia, tumor of the cord ?	61	132/66	0	0	0	0	0	0	0	0	±	+++	0	0	0	0	Doubtful retinal arteriosclerosis
168	Diabetes, colitis, 1 year	58	130/0	0	0	0	0	0	0	0	0	+	+++	0	0	0	0	Doubtful retinal arteriosclerosis
169	Diabetes ?	63	136/96	0	0	0	0	0	0	0	0	±	++	0	0	+	+	Definite retinal arteriosclerosis
170	Diabetes, obesity ?	60	138/88	0	0	0	0	0	0	0	+	0	0	0	0	++	++	Definite retinal arteriosclerosis
171	Diabetes ?	60	138/82	0	0	0	0	0	+	0	+	++	++	0	0	++	0	Definite retinal arteriosclerosis, buff spots
172	Diabetes, arteriosclerosis 8 years	42	138/82	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
173	Diabetes, arteriosclerosis 20 years	62	144/82	0	0	0	0	+	++	0	++	++	+++	0	0	++	0	Definite retinal arteriosclerosis, buff spots, small, round hemorrhages
174	Diabetes 8 years	60	144/82	0	0	0	0	+++	++	0	+	±	+++	0	0	++	0	Definite retinal arteriosclerosis, beginning "diabetic retinitis"

TABLE 3.—*Changes in Eyeground in Forty-Seven Patients with Diabetes—Continued*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
175	Diabetes, arteriosclerosis 7 to 8 years	64	141/60	0	0	0	0	0	0	0	0	++	+++	0	0	+	0	Definite retinal arteriosclerosis
176	Diabetes, obesity 5 years	51	144/90	0	0	0	0	+	++	0	0	++	+++	0	0	+	0	Definite retinal arteriosclerosis, cataract in the left eye, small superficial hemorrhages, beginning "diabetic retinitis" macular fan
177	Diabetes ?	43	146/82	0	0	0	0	0	0	0	0	++	+	0	0	0	++	Definite retinal arteriosclerosis, nonmedullated nerve fibers
178	Diabetes 2 years	57	152/96	0	0	0	0	0	0	+	+	+++	++	0	0	++	0	Definite retinal arteriosclerosis
179	Diabetes, arteriosclerosis 6 years	54	156/78	0	0	0	0	0	0	0	+	+++	++	0	0	++	+	Definite retinal arteriosclerosis, beginning bilateral cataract
180	Diabetes ?	52	156/80	0	0	0	0	0	0	0	0	0	++	0	0	0	++	No retinal arteriosclerosis
181	Diabetes 1 year	44	158/96	0	0	0	0	++	0	0	+++	+	++ ++	0	0	+++	0	Definite retinal arteriosclerosis, small, round hemorrhages
281	Diabetes 9 years	44	158/96	±	0	0	0	0	0	0	0	+	+	0	0	++	0	Definite retinal arteriosclerosis
183	Diabetes, arteriosclerosis 3 to 4 years	63	162/88	0	0	0	0	+++	++	+	++	0	++	0	0	++	++	Definite retinal arteriosclerosis, "diabetic retinitis," small, round hemorrhages, yellowish white spots
184	Diabetes ?	60	174/96	0	0	0	0	0	0	0	0	++	+++	0	0	++	++	Definite retinal arteriosclerosis
185	Diabetes, myocarditis and hypertension 11 years	56	192/108	0	+	0	0	0	0	0	0	+	0	0	0	+	0	Definite retinal arteriosclerosis, retinas red and hazy
186	Diabetes 11 years	53	196/102	0	0	0	0	0	0	0	0	+	+	++	0	0	0	Doubtful retinal arteriosclerosis
187	Diabetes, arteriosclerosis 1 year	68	214/98	0	0	0	0	++	0	0	0	+	++	0	0	+	0	Definite retinal arteriosclerosis, large, round hemorrhages

found that a large majority exhibit a diabetic curve. He suggests that all patients with hypertension are at least potentially diabetic patients, and that sclerosis of the vessels of the pancreas with resulting insufficiency of the islands is the probable explanation for the increase in blood sugar.

In the group examined in this study, the average age of diabetic patients with definite retinal arteriosclerosis was 57.5 years, while in those showing doubtful or no retinal arteriosclerosis, the average age was 33. Definite or doubtful arteriosclerosis did not occur in any patient under 30 years of age. If the presence of retinal arteriosclerosis is a sign of sclerosis of small vessels in other parts of the body, this appears to indicate that sclerosis of small vessels may be a factor in the production of diabetes after 50 years of age; it is, at least, a common occurrence. Sclerosis of the small vessels does not appear to be a necessary factor in the production of diabetes in the young person. Some degree of sclerosis of the choroidal vessels and chorioretinitis was present in 40 per cent of the cases. Adam [8] mentions diabetes as an

TABLE 4.—*Retinal Arteriosclerosis in Group II*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	31.6	13.9	50.0
With hypertension	81.8	9.1	9.1

occasional cause of this condition; it is found with greater frequency in the diabetic group than in the other groups included in this series.

Changes in the disk were infrequent as compared with changes in the eyeground in hypertension and nephritis, only two cases showing definite papilledema. There were other causes for the changes in the disk observed in the series of diabetic cases. In case 157, there was an old papilledema with secondary atrophy, accompanied by marked vascular sclerosis and retinal change, while in case 165 there was a question of tumor of the brain associated with the diabetes. Shafer [9] and Grafe [10] both comment on the absence or infrequency of papilledema in diabetes.

Not counting small deposits of pigment, eleven of forty-seven cases of diabetes showed some abnormal retinal changes. Eight cases showed small, round hemorrhages in the deeper layers of the retinas; in one instance, case 187, there was a single, large, round hemorrhage. In contrast to this, only two cases showed superficial flame-shaped or

8. Adam, Curt.: Ophthalmoscopic Diagnosis, Berlin, 1913, trans. by Matthias L. Foster, New York, Rodman Co., 1913, 229 pp., 48 pl.

9. Shafer, J. J.: Diabetic Retinitis, Am. J. Surg. **32**:67 (March) 1918.

10. Volhard, quoted by Grafe, E.: Changes of the Retinae in Diabetes, Klin. Wchnschr. **2**:1216 (June 25) 1923.

irregular hemorrhages. Four cases (163, 174, 176 and 183) showed small yellowish-white spots or macular fan formation (or incomplete macular star) in the central portion of the retinas. This type of retinitis, together with small, round hemorrhages, is considered by many observers as characteristic of "diabetic retinitis." In two cases, 163 and 176, there was beginning fan formation. In every instance, the patients who had retinitis were above 40 years of age and had definite retinal arteriosclerosis. Three had a systolic blood pressure above 145 mm. at the time of examination.

There is some diversity of opinion as to whether or not diabetes in itself produces characteristic retinal changes. Wagener and Wilder [11] state that retinitis does not occur in uncomplicated diabetes. Volhard (quoted by Grafe [10]) says that he has never seen diabetic retinitis when it was not associated with hypertension. Garrod [12] states that diabetic retinitis occurs only in elderly patients, while Bardsley [13] calls attention to two cases seen by him in patients 26 and 35 years of age. The first patient had a normal blood pressure.

The prevailing opinion, and probably the correct one, is that expressed by Garrod,[12] Friedenwald,[14] Grafe [10] and Wagener;[11] that vascular change and hypertension are the factors of primary importance in the production of diabetic retinitis, while hyperglycemia and metabolic disturbance are of secondary importance and responsible for the individual characteristics.

From the visual impressions that I have retained after examining this group of diabetic patients, I would say that the following appearances suggest diabetic retinitis: (1) a retina that is redder than normal, with a brilliant arterial reflex; (2) the presence of small, round hemorrhages which appear through the ophthalmoscope to be from 1 to 2 mm. in diameter; (3) small, discrete, yellowish-white and grayish-white spots seen in groups on the central field of the retina; (4) fan formation; (5) retinal arteriosclerosis with disks that appear normal or nearly normal, and (6) some degree of sclerosis of the choroidal vessels in the periphery.

GROUP III: OBSERVATIONS ON THE EYEGROUND IN ACUTE AND IN SUBACUTE NEPHRITIS

The opportunity to examine a large number of patients with acute and subacute nephritis did not present itself during the period of study, because a majority of the patients in the medical wards had reached

11. Wagener, H. P., and Wilder, R. M.: Retinitis of Diabetes Mellitus, J. A. M. A. **76**:515 (Feb. 19) 1921.

12. Garrod, Sir Archibald: Diabetes in Relation to Diseases of the Eye, Arch. Ophth. **1**:378 (July) 1921.

13. Bardsley, P. C.: Ibid., p. 384. (Discussion of Garrod's paper.)

14. Friedenwald, H.: Diabetic Retinitis, J. A. M. A. **85**:428 (Aug. 8) 1925.

TABLE 5.—*Changes in the Eyeground in Nine Cases of Subacute Nephritis*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
72	Acute hemorrhagic nephritis	13	118/72	0	0	0	0	0	0	0	0	0	++	0	0	0	0	No retinal arteriosclerosis, bright red arteries probably normal for age
73	Acute nephritis	18	154/94	0	0	0	0	0	0	0	0	0	0	0	0	0	+	No retinal arteriosclerosis
74	Subacute nephritis	30	106/78	0	0	0	0	0	0	0	0	0	+	+	0	0	0	No retinal arteriosclerosis
75	Subacute nephritis	46	108/78	0	0	0	0	0	+	0	0	0	++	0	0	0	0	No retinal arteriosclerosis, buff spots
76	Subacute nephritis with edema	43	115/80	+	0	0	+	0	0	0	++	++	+++	+	+	++	++	Definite retinal arteriosclerosis
77	Subacute nephritis	13	128/66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
78	Subacute hemorrhagic nephritis	16	132/86	0	0	0	0	0	0	+	0	±	++	0	0	0	0	Doubtful retinal arteriosclerosis
79	Subacute nephritis	38	134/78	++	+	..	++	0	+++	+	++	++	+++	+	++	++	0	Definite retinal arteriosclerosis, cotton and soft grayish white spots
80	Subacute nephritis with edema, renal insufficiency	20	160/92	0	0	0	++	++++	+	0	0	++	++	0	0	0	0	Definite retinal arteriosclerosis, flame shape hemorrhages, gray white and hard white spots

an age when acute nephritis is rather uncommon. However, nine cases were studied, and the results are given in table 5. Three patients showed definite arteriosclerosis, including two patients with definite hypertension. Case 76 is interesting because the patient always had a normal or low blood pressure during the long period that he was under observation. He also had marked albuminuria with a large number of fatty casts and marked edema, a low basal metabolism and a practically normal renal function, except for a slightly diminished phthalein output. Clinically, his condition resembled nephrosis. It was difficult to explain his retinal arteriosclerosis. Later inquiry into his previous medical history, however, revealed the fact that prior to his admission to the Peter Bent Brigham Hospital he had twice been a patient in the Massachusetts General Hospital on account of hypertension. His record there showed that his blood pressure readings varied between 130

TABLE 6.—*Summary of Changes in Eyegrounds in Groups IV and V*

	Chronic Nephritis 20 Cases	Vascular Hypertension 20 Cases
Disk papilledema	15	10
Increased vascularity	14	6
Hemorrhage	1	1
Retinal edema	14	4
Hemorrhages	16	9
Buff, gray-white, yellowish white and white spots, powdery spots	12	11
Cotton wool spots	4	3
Macular fan or star	8	2
Definite retinal arteriosclerosis	13	17
Sclerosis of choroidal vessels	6	6
Examination of vessels unsatisfactory because of retinal edema, high refractive error, etc.	3	2
Arteriosclerotic change in macula	2	0
Retinal detachment	2	0

systolic and 80 diastolic and 170 systolic and 110 diastolic. Since I left the Peter Bent Brigham Hospital, this patient has undergone a decapsulation operation. Dr. O'Hare, in a recent communication, states that a biopsy specimen removed at operation showed nephrosis with glomerulitis.

With the exception of one patient with slight papilledema and retinal edema, the retinal changes in patients with nonhypertensive nephritis were negligible. Retinitis was present in only two cases (79 and 30); both patients had hypertension.

GROUPS IV AND V: CHANGES IN THE EYEGROUND IN CHRONIC NEPHRITIS AND IN VASCULAR HYPERTENTION

The changes in the cases of the patients with chronic nephritis and vascular hypertension are interesting when compared with one another. A summary of the important changes is seen in table 6. Before commenting on the changes, perhaps I should mention that the majority of these patients had either severe nephritis or severe hypertension and

were admitted to the hospital because they showed symptoms which made us feel that it was not safe to allow them to continue as ambulatory patients. Their condition, therefore, was usually of long standing.

A study of the tables shows that the incidence of papilledema, retinal edema, hemorrhage, macular fan and star formations, arteriosclerotic degeneration in the macular region and retinal detachment was greater in patients with chronic nephritis than in those with hypertension.

Two views are held concerning the production of papilledema in nephritis and hypertension. Larsson [15] believes that it is a manifestation of increased intracranial pressure. He cites the cases of eleven patients with papilledema, all of whom had an increased cerebrospinal fluid pressure, varying from 200 to 600 mm. In two of five cases in which spinal drainage was performed, there was temporary improvement in vision and choking was less marked; in the other cases, there was no improvement, or the visual impairment was increased. Larsson quotes von Hippel's statement that increased lumbar pressure is necessary in choked disk, and that it practically does not exist in the absence of it. Volhard [16] states that the whole picture of nephritis "neuroretinitis" can be explained on the basis of arterial ischemia.

Moore [2] considers edema of the disk and the secondary atrophy due to disease of the vessels and their inability to transmit an efficient supply of blood.

I cannot express an opinion as to which of the foregoing two factors is operative in the production of papilledema. Spinal drainage was resorted to in case 88. The choking was marked, and long hemorrhages were radially arranged around the disk, not unlike the petals of the dahlia. Daily observation of the eyeground did not show any change in the retinal edema and papilledema after the lumbar puncture, and the patient's condition became definitely worse. For this reason, there was some hesitation in the further application of this method as a therapeutic procedure.

In commenting on the retinal changes that take place as a result of nephritis, I adhere purposely to the somewhat nondescript designation of "spots," instead of referring to them as retinal exudates With the exception of cotton wool spots, the retinal changes are probably due to a fatty or hyaline degenerative process or in some instances of colloid deposits.

Moore [17] states that pathologic processes of the most diverse origin will produce white spots or areas in the retina. Adam [8] is of essentially

15. Larsson, S. W.: Choked Disc in Nephritis, Acta Ophth. **1**:193, 1924.

16. Volhard: Die doppelseitigen hamatogenen Nierenerkrankungen, Staehelin, Handbuch der inneren Medizin **3**:2, 1918; quoted by Larsson (footnote 14).

17. Moore, R. F. Medical Ophthalmology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1922, p. 178.

the same opinion concerning their origin, but also believes that fatty degeneration is the principal cause. Semple [18] and Duvigneaud [19] consider cotton wool spots to be, at least at the time of their appearance, a network of fibrinous exudate. Moore [2] has found cotton wool spots, particularly in those cases in which the toxic element of nephritis is prominent. The various degenerative spots are most probably due to ischemia of portions of the retina following changes in the retinal vessels which result in a diminished vascular supply; the cotton wool spots, if caused by a toxic element, may be due to exudation resulting from the action of the toxin on the endothelial lining of the retinal capillaries.

While the significance of the buff spot is not understood, the fact that it was observed with greater frequency than the other varieties of spots and that it also occurred when no other spots were present may indicate that it is the forerunner or any early stage of the other degenerative spots. However, I have not seen these buff spots actually change to gray-white or white spots. The fine "powdery" white spots, or exudate as termed by Moore, were seen in cases 86, 90 and 91. He interprets their presence as indicating a subsidence of the retinitis.[2] He reports a case in which there was a complete disappearance of the retinitis when the patient was examined seven and one-half years later, at the time of death, which was due to the development of uremia. He believes that retinitis is a self-limited condition, and that a patient who has once had retinitis is protected against further recrudescence.

Tresilian [20] also reports a case of a boy, aged 15, who had subacute nephritis, edema, marked albuminuria, papilledema and albuminuric retinitis with macular fan when this author first saw him. Tresilian did not see the patient again until six years later, at the time of his death from uremia. Retinitis was not present nor was there any record of the blood pressure or blood chemistry.

When I examined the patient in case 86 nine months later, the "powdery" white spots and well developed fan had almost completely disappeared.

Cotton wool spots were found in three cases of hypertension (107, 109 and 116). The patient in case 109 developed a sudden renal insufficiency and died about six weeks later. At the time of his retinal

18. Semple, N. M.: Some Questions Concerning the Method of Development and the Pathology of the Retinitis of Bright's Disease, Am. Path. Soc. **12**:817, 1909-1911.

19. Rochon-Duvigneaud: Albuminuric Retinitis, Ophth. Rev. **31**:307, 1912; quoted by Benedict (footnote 22).

20. Tresilian, F.: Albuminuric Retinitis as a Prognostic Sign, Brit. M. J. **1**:148 (Jan. 27) 1923.

examination, he had normal renal function. At present it is not possible to trace the fate of the other two patients.

In five of eight cases of chronic nephritis in which a macular star or fan was seen, my notes state that it was coarse; in the other three, its appearance was not noted; in vascular hypertension, the fan was described as fine in one instance; in the other, no special note was made. Moore [2] states that in arteriosclerotic retinitis and renal retinitis, the star or fan may be present in either case; but that in the former the star is composed of small dots, while in the latter the dots are larger, less discrete and tend to coalesce and form ragged and irregular rods, with edema usually present. My impressions, gathered from further observations, lead me to believe that the lines in the star or fan, when it is present in vascular hypertension, are likely to be more finely "penciled." While in the individual case it may be impossible to tell whether nephritis exists in a patient with hypertension, examination of the eyeground will reveal certain changes which occur with greater incidence when nephritis is present, as is brought out in tables 7 and 8. When one takes into consideration the fact that the group of patients with nephritis includes two with normal tension and that the condition of the vessels was more difficult to determine, particularly because of more marked retinal edema, it will be seen that the incidence of retinal arteriosclerosis is about the same. When there are only one or two definite venous compressions, or the irregularity of lumen is confined to one or two vessels, retinal arteriosclerosis may, under these conditions, easily be overlooked. It is Moore's opinion [2] that vascular disease is less of a feature in renal retinitis. Only one patient (case 99) showed definite phlebosclerosis. Sclerosis of the choroidal vessels was observed in six cases in which hypertension and nephritis, were also present. With two exceptions, it occurred in association with definite retinal arteriosclerosis.

Arteriosclerotic changes in the macula with a collection of buff spots and later retinal degeneration with pigmentation were observed in three cases of nephritis; namely, cases 84, 94 and 100. Adam [8] believes that the spots are due to a colloid deposit and later, degeneration produced by vascular change in the blood supply of the macula. This is usually supposed to be a senile change, but in cases 84 and 100 the patients were 36 and 37 years of age.

In cases 90 and 99, the patients exhibited detachment of the retina.

"Guttate" choroiditis, showing isolated collections of yellow spots, was seen in one case (106); the patient was 65 years of age. This is considered to be a senile change.

My impression concerning retinitis in hypertension and nephritis is that while the underlying cause is the same, namely, vascular change, the more rapid rate of progression in the retinitis of nephritis is probably

TABLE 7.—*Changes in the Eyeground in Cases of Nephritis and Vascular Hypertension*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
81	Chronic nephritis with edema	18	110/78	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
82	Chronic nephritis with edema	62	126/78	0	0	0	0	0	++	+	0	+	++	0	0	±	0	Doubtful retinal arteriosclerosis, grayish-white and buff spots
83	Chronic nephritis with edema	20	165/90	++	+	0	+	+	++	0	0	+	++	0	+	0	++	Doubtful retinal arteriosclerosis, superficial hemorrhages, white spots above macula
84	Chronic nephritis, hypertension	36	166/124	+++	+	0	+++	++ ++	++ ++	0	++	+++	++	0	+	++	0	Definite retinal arteriosclerosis, many superficial hemorrhages, cotton wool, grayish-white and buff spots about macula
85	Chronic nephritis, uremia	60	180/104	0	0	0	0	0	++	++ ++	0	+++	+++	++	0	+++	+++	Definite retinal arteriosclerosis, extensive chorioretinitis
86	Chronic nephritis, hypertension	32	192/ 18	0	0	0	0	0	+++	0	—	—	—	—	+	—	—	Well developed macular fan and "powdery" white spots, largely disappeared after 9 months, high degree myopia, examination of vessels unsatisfactory
87	Chronic nephritis with edema, hypertension	23	196/114	+++	++	0	++	++	++ ++	+	0	+++	++	0	+	++	0	Definite retinal arteriosclerosis, superficial hemorrhages, cotton wool and grayish-white spots
88	Chronic nephritis with edema hypertension	57	198/104	++ ++	+	++ ++	++ ++	++ ++	+++	0	0	++ ++	+++	0	++	++	0	Definite retinal arteriosclerosis, "dahlia" retinas, cotton wool spots
89	Chronic nephritis with edema, ' pertension	34	204/120	+++	+	0	+++	++	+++	0	+++	0	+++	++	++	+++	0	Definite retinal arteriosclerosis, large subhyaloid "boat-shaped" hemorrhages, coarse macular star

90	Chronic nephritis, hypertension	22	208/114	++ ++	0	0	++ ++	+	++ ++	+	—	—	—	+	+	—	0	Detachment of retinas, due to marked edema, coarse macular star, "powdery" white spots
91	Chronic nephritis, hypertension	50	210/106	+	0	0	0	++	+++	0	++	0	++ ++	0	0	++	0	Definite retinal arteriosclerosis, superficial hemorrhages, cotton wool and "powdery" white spots, copper wire arteries
92	Chronic nephritis	44	216/ 34	+	0	0	0	++	+++	++	+++	+++	+	0	0	+++	+	Definite retinal arteriosclerosis, cotton wool spots and macular fan
93	Chronic nephritis with edema	39	224/138	+	+	0	+	++	0	0	+++	+	++	0	0	±	0	Doubtful retinal arteriosclerosis, flame shaped hemorrhages
94	Chronic nephritis, hypertension	57	232/140	+++	+	0	+	++	++	++	++ ++	+++	+++	0	++	+++	0	Definite retinal arteriosclerosis, flame shaped hemorrhages; beginning chorioretinitis macular region
95	Chronic nephritis with edema, hypertension	50	232/144	+++	+	0	+++	+++	++ ++	0	+	—	—	—	+	—	0	Superficial hemorrhages, cotton spots, coarse macular star; vessels could not be seen satisfactorily on account of edema
96	Chronic nephritis, uremia, hypertension	47	234/110	++	++	0	+++	++	+++	0	0	++	++	0	0	+	0	Definite retinal arteriosclerosis, macular fan
97	Chronic nephritis, hypertension	54	234/136	+++	+	0	+++	++	0	0	+	+++	++	++	+	+++	++	Definite retinal arteriosclerosis, marked phlebosclerosis
98	Chronic nephritis, hypertension	39	234/154	0	+	0	+	++ ++	++ ++	0	++	++	+++	0	+	+++	0	Definite retinal arteriosclerosis, macular fan, dagger hemorrhages, copper wire arteries
99	Chronic nephritis, hypertension	49	254/156	+++	++	0	++	++ ++	++ ++	++	++	+++	+	++ ++	+++	+++	++	Definite retinal arteriosclerosis, detached retina, coarse macular star, phlebosclerosis
100	Chronic nephritis, hypertension	37	272/160	+++	++	0	+++	++ ++	++ ++	++	++	++	++	++	++	0	++	Definite retinal arteriosclerosis, chorioretinitis macular region

TABLE 8.—*Changes in the Eyeground in Cases of Nephritis and Hypertension*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
101	Hypertension, arteriosclerosis	62	152/ 80	0	0	0	0	0	++	++	0	+	+++	0	0	+	++	Doubtful retinal arteriosclerosis, buff and grayish-white spots
102	Hypertension, chronic bronchitis	55	164/ 88	0	+	0	0	0	0	0	+	++	+++	0	++	+	0	Definite retinal arteriosclerosis
103	Hypertension, arteriosclerosis	42	170/110	0	0	0	0	0	0	0	+	+++	+++	0	0	++	++	Definite retinal arteriosclerosis
104	Hypertension. arteriosclerosis	53	174/118	0	0	0	0	0	0	0	0	+++	++	0	0	++	0	Definite retinal arteriosclerosis
105	Hypertension, arteriosclerosis, myocarditis	54	182/ 84	+	+	0	0	+	0	0	+	++	++	+++	++	+++	++	Definite retinal arteriosclerosis
106	Hypertension, arteriosclerosis	65	186/ 88	0	0	0	0	0	+++	+	0	++	+++	0	++	++	0	Definite retinal arteriosclerosis, guttate choroiditis
107	Hypertension, angina pectoris, arteriosclerosis	51	188/108	+	0	0	+	+++	+++	++	+++	+	+++	0	++	+++	0	Definite retinal arteriosclerosis, superficial hemorrhages, cotton wool and grayish-white spots
108	Hypertension, chronic myocarditis	39	196/128	0	0	0	0	0	+	+	+++	+	++ ++	0	0	++	0	Definite retinal arteriosclerosis; buff spots; copper wire arteries
109	Hypertension, periarteritis nodosa	22	208/130	++	+	+	+++	++	+++	0	0	—	+++	0	+++	0	0	Superficial hemorrhages, cotton wool spots and fan; examination of vessels unsatisfactory on account of retinal edema

110	Hypertension, myocarditis; retinal arteriosclerosis	59	206/146	+	0	0	0	+++	0	0	0	+++	+	0	0	+++	+++	Definite retinal arteriosclerosis
111	Hypertension, arteriosclerosis	74	216/ 88	0	0	0	0	0	0	0	0	++	+++	0	++	++	0	Definite retinal arteriosclerosis
112	Hypertension. myocarditis, arteriosclerosis	56	218/ 88	0	0	0	0	0	0	0	++	++	++ ++	0	0	++ ++	0	Definite retinal arteriosclerosis; copper wire arteries
113	Hypertension, arteriosclerosis	55	222/108	0	0	0	0	0	++	0	+++	++	+++	0	0	+++	0	Definite retinal arteriosclerosis, buff spots
114	Hypertension, myocarditis	60	232/122	+	+	0	0	0	+	0	+++	++	+++	0	0	+++	+++	Definite retinal arteriosclerosis
115	Hypertension, arteriosclerosis, myocarditis	55	236/120	+	0	0	0	++	+	0	++	++ ++	++ ++	+	0	++ ++	0	Definite retinal arteriosclerosis, superficial hemorrhages, copper wire arteries
116	Hypertension, arteriosclerosis	44	240/146	0	0	0	0	++	++	0	++	+++	+++	0	++	++	0	Definite retinal arteriosclerosis, superficial hemorrhages, cotton wool spots; perivascular exudation
117	Hypertension, myocarditis, nephritis	50	242/150	+++	++	0	+++	+++	+++	0	++	+++	++ ++	0	++	+++	0	Definite retinal arteriosclerosis, superficial and irregular hemorrhages; penciled fan; copper wire arteries
118	Hypertension, arteriosclerosis	54	242/126	+	0	0	0	0	0	0	0	++	++	0	0	+++	+++	Definite retinal arteriosclerosis
119	Hypertension	29	252/160	++	0	0	++	++	+	—	—	—	—	—	++	—	—	Yellow white spots; high degree of myopia; vessels could not be examined
120	Hypertension, arteriosclerosis, chronic nephritis	57	.....	+	+	0	0	+	++	0	+	+++	+++	0	0	+++	0	Definite retinal arteriosclerosis, superficial hemorrhages; buff spots

responsible for such differences in appearance as exist. The frosted window pane in the bedroom shows more delicately traced figures than that in the kitchen, where the humidity is higher and the heat greater and the frosting proceeds at a more rapid rate. The rate of formation may account for the difference in appearance of the macular fan or star.

The consensus of opinion is that the retinitis of chronic nephritis is due either to retinal arteriosclerosis alone or to retinal arteriosclerosis plus an added toxic, or rather an unknown toxic, factor. In addition to authorities already quoted, the former view is held by Schieck and Volhard;[21] those inclined to the latter view are Benedict,[22] Wagener,[11] Spir[23] and Ramsey.[24]

Behan,[25] quoting Bulson,[26] disagrees with Benedict in that he believes that hypertension is the most prominent factor in the production of retinitis. He cites a case[27] of toxemia of pregnancy in which he saw the formation of macular star occur in two weeks. However, there is no statement to the effect that the patient had a normal blood pressure before the onset of the toxemia. Later in his article, he makes the rather remarkable admission that he finds 87 per cent of retinal vascular change and 100 per cent of retinal degeneration accompanied by hypertension. On the basis of Behan's figures, it is difficult to comprehend how he finds it possible to deny a relationship between vascular hypertension and retinal arteriosclerosis and retinitis. To sustain his position, he calls attention to the fact that about 20 per cent of the patients with retinal arteriosclerosis do not have hypertension. It is probable that if the previous vascular history of these patients were known, it would be disclosed that at some time they had a hypertension.

The question as to whether retinal arteriosclerosis precedes or is secondary to hypertension is still debatable. It is impossible to draw any conclusion from the cases included in this study. I have recently had

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21. Schieck, F., and Volhard, F.: Netzhautveranderungen und Nierenleiden, Zentralbl. f. d. ges. Ophth. **5**:465, 1921; quoted by Benedict (footnote 22).

22. Benedict, W. L.: Retinitis Associated with Disease of the Cardiovascular System, New York M. J. **117**:741 (June 20) 1923. Retinitis of Hypertension Plus Nephritis, J. A. M. A. **78**:1688 (June 3) 1922.

23. Spir, E.: Retinitis in Chronic Nephritis, München Med. Wchnschr. **72**: 1030 (June 19) 1925; abstr. J. A. M. A. **85**:556 (Aug. 15) 1925.

24. Ramsey, A. Maitland: The Significance of Albuminuric Retinitis in Chronic Renal Cirrhosis, Practitioner, **114**:354 (May) 1925.

25. Behan, J. L.: The Fundus Changes in Nephritis, J. A. M. A. **78**:1691 (June 3) 1922.

26. Bulson, A. E., Jr.: Abstract of Discussion of Paper by George Slocum; A Study of Ophthalmoscopic Changes in Nephritis, J. A. M. A. **67**:5 (July 1) 1916.

27. Behan, J. L.: Proceedings Eye Section, New York State Med. Soc., April, 1922; quoted in footnote 25.

under observation two patients with the nephritic type of toxemia of pregnancy during their first pregnancy who had normal blood pressures during the first months, one of whom did not show any vascular change until she had had a markedly elevated blood pressure for from three to four months. The second patient had marked vascular changes six weeks after delivery of a seven months' fetus, at which time she had hypertension. In the first case, the fundi were examined frequently, but in the second case, only one observation was possible. As the patient did not give a history of nephritis, and as she had a normal blood pressure during the first months of her pregnancy, it may be assumed that the retinal arteriosclerosis manifested itself within a period of five months.

Benedict [22] states that it is clearly evident that hypertension may be present long before changes in the retinal vessels take place. He says:

> In a great many persons having essential hypertension with a diastolic pressure of 160 or more and a systolic pressure of more than 200, the retinal vessels show not a single sign of thickening or other change.

As Benedict has access to a large clinical material which includes many ambulatory hypertensive patients, his opinion must be accorded considerable weight. However, the observations of O'Hare and Walker [1] and my observations in this series would indicate that while the number of these cases observed by Benedict may have been considerable on account of his large amount of material, the actual percentage in total cases studied may have been small. A small series of cases studied over a long period in which the date of onset of hypertension is definitely known will do much to answer this question.

GROUPS VI AND VII: THE CHANGES IN THE EYEGROUND IN PATIENTS WITH CARDIAC DISEASE

The sixth group to be considered is the group of patients with chronic myocarditis or chronic myocardial degeneration, with or without hypertension, developing on a vascular basis, alone or combined with generalized arteriosclerosis; and patients with arrhythmia, angina pectoris and cardiac infarction. Chronic myocarditis was either the primary or the important secondary clinical diagnosis in this group.

To contrast with this group of patients with chronic myocardial disease is a group with chronic valvular disease. As far as could be determined, the cardiac disability in all of these cases developed on a rheumatic basis.

These groups comprise, respectively, fifty-six and fifteen cases, and the data are tabulated in table 9. In group VI, the fifty-six cases are arranged according to the level of the systolic blood pressure at the time of examination. This group is subdivided as follows: (1) twenty-two

TABLE 9.—*Changes in the Eyeground in Cardiac Cases*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
1	Cardiac infarction, chronic myocarditis	53	102/74	0	0	0	0	0	+	0	+	0	++	0	0	±	+++	Doubtful retinal arteriosclerosis, few small buff spots
2	? Cardiac infarction, chronic myocarditis	64	106/64	0	0	0	0	0	0	0	+	±	0	0	0	+	0	Definite retinal arteriosclerosis
3	Angina pectoris, chronic myocarditis	53	108/96	0	0	0	0	0	0	0	++	+++	+	0	0	0	0	Definite retinal arteriosclerosis
4	Cardiac infarction, chronic myocarditis	70	114/88	+	0	0	0	0	0	++	0	+	+	0	+	+++	++	Definite retinal arteriosclerosis, beginning chorioretinitis
5	Chronic myocarditis, angina pectoris	56	114/74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	None
6	Chronic myocarditis, angina pectoris	58	114/74	0	0	0	0	0	0	0	0	±	0	0	0	0	0	Doubtful retinal arteriosclerosis
7	Chronic myocarditis, arteriosclerosis	45	118/74	0	0	0	0	0	0	0	+++	±	+++	0	0	++	0	Definite retinal arteriosclerosis
8	Chronic myocarditis, arteriosclerosis	52	122/76	0	0	0	0	0	0	0	+	±	++	0	0	±	0	Doubtful retinal arteriosclerosis
9	Chronic myocarditis, auricular fibrillation	70	122/74	0	0	0	0	0	++	0	0	++	++	0	0	0	+++	Definite retinal arteriosclerosis, guttate choroiditis
10	Cardiac infarction, chronic myocarditis	64	124/30	0	0	0	0	0	0	0	0	±	+	0	0	±	0	Doubtful retinal arteriosclerosis
11	Chronic myocarditis, arteriosclerosis	58	130/68	0	0	0	0	0	0	0	0	++	+++	0	0	++	0	Definite retinal arteriosclerosis
12	Chronic myocarditis, angina pectoris	44	136/76	0	0	0	0	0	0	0	0	±	±	0	0	0	0	Doubtful retinal arteriosclerosis
13	Chronic myocarditis, arteriosclerosis	57	136/76	±	0	0	0	0	0	0	0	+	0	0	0	++	+	Definite retinal arteriosclerosis
14	Chronic myocarditis, auricular flutter	65	136/94	0	0	0	0	0	0	0	0	±	++	0	0	+	0	Definite retinal arteriosclerosis
15	Chronic myocarditis, auricular fibrillation	52	138/86	0	0	0	0	0	0	0	+++	++	+++	++	++	+++	0	Definite retinal arteriosclerosis
16	Chronic myocarditis, auricular fibrillation	65	138/74	0	0	0	0	0	+	++	0	+	++	0	0	+++	++	Definite retinal arteriosclerosis, buff spots
17	Chronic myocarditis, chronic bronchitis	56	140/84	0	0	0	0	0	0	+++	0	+	+++	0	0	+	+++	Definite retinal arteriosclerosis, chorioretinitis
18	Chronic myocarditis, auricular fibrillation	72	142/70	0	0	0	0	0	0	0	0	+	0	0	0	++	0	Definite retinal arteriosclerosis
19	Chronic myocarditis, arteriosclerosis	65	142/78	0	+	0	0	0	0	0	+	+++	++	0	0	+++	0	Definite retinal arteriosclerosis
20	Chronic myocarditis, arteriosclerosis	52	142/88	0	0	0	0	0	0	0	0	+	0	0	0	++	0	Definite retinal arteriosclerosis
21	Angina pectoris, chronic myocarditis	47	142/92	0	0	0	0	0	0	0	0	+	++	0	0	+	0	Definite retinal arteriosclerosis

22	Chronic myocarditis	42	144/102	0	0	0	0	0	0	0	0	±	++	0	0	0	0	Doubtful retinal arteriosclerosis
23	Cardiac infarction, chronic myocarditis, hypertension	57	146/94	+	+	0	0	0	0	0	0	±	+++	0	+++	++	+++	Definite retinal arteriosclerosis
24	Chronic myocarditis, hypertension, arteriosclerosis	60	148/0	0	0	0	0	0	++	0	+	++	0	0	0	++	0	Definite retinal arteriosclerosis; buff and gray spots; variation in intensity of arterial reflex
25	Chronic myocarditis, auricular fibrillation, hypertension	74	148/76	0	0	0	0	0	0	0	0	+++	+++	0	0	++	+++	Definite retinal arteriosclerosis, beginning cataracts, bilateral
26	Chronic myocarditis, hypertension	70	152/74	+	+	0	0	0	0	+	0	0	+	0	0	0	++	Doubtful retinal arteriosclerosis, narrow vessels
27	Chronic myocarditis, auricular fibrillation, hypertension	70	156/88	0	0	0	0	0	0	0	+	++	++	0	0	0	++ ++	Definite retinal sclerosclerosis, cataract in the right eye
28	Chronic myocarditis, angina pectoris, hypertension	58	158/100	0	0	0	0	+	0	0	+	++	+++	++	0	++	0	Definite retinal sclerosclerosis, large flame shape hemorrhage
29	Chronic myocarditis, arteriosclerosis, hypertension	63	160/72	0	0	0	0	0	++	0	++	++	++	0	0	++	0	Definite retinal arteriosclerosis, definite phlebosclerosis, buff spots
30	Chronic myocarditis, hypertension	70	160/90	0	0	0	0	0	0	0	0	++	+	0	0	+	0	Definite retinal arteriosclerosis
31	Chronic myocarditis, premature ventricular beats, arteriosclerosis and hypertension	57	164/78	0	+	0	0	0	0	0	0	++	++	0	0	++	0	Definite retinal arteriosclerosis
32	Chronic myocarditis, hypertension	60	164/22	0	0	0	0	0	0	0	0	+	+	0	0	++	0	Definite retinal arteriosclerosis
33	Chronic myocarditis, nephritis, hypertension	72	166/88	0	0	0	0	0	0	0	+++	++	+++	+++	++	+++	0	Definite retinal arteriosclerosis
34	Chronic myocarditis, angina pectoris, hypertension	63	166/0	0	0	0	0	0	0	0	++	+	+++	0	+	+++	+	Definite retinal arteriosclerosis
35	Chronic myocarditis, auricular fibrillation, hypertension	52	166/100	0	0	0	0	0	0	0	+	+++	+++	0	0	0	0	Definite retinal arteriosclerosis, marked irregularity in lumen; almost complete obliteration in one artery, no compression effects
36	Chronic myocarditis, arteriosclerosis, hypertension	65	172/90	0	0	0	0	0	0	0	++	++	+++	0	0	++	0	Definite retinal arteriosclerosis
37	Chronic myocarditis, hypertension	54	176/102	0	0	0	0	0	0	0	++	++	+++	0	+	+++	0	Definite retinal sclerosclerosis
38	Chronic myocarditis, auricular fibrillation, hypertension	53	176/100	0	0	0	0	0	+	0	+++	±	+++	0	+	+++	++	Definite retinal sclerosclerosis, yellowish white spots
39	Chronic myocarditis, auricular fibrillation, hypertension	54	178/102	0	0	0	0	++	0	++	0	++	++ ++	+	+	++	0	Definite retinal arteriosclerosis, beginning degeneration in macular region

TABLE 9.—*Changes in the Eyeground in Cardiac Cases—Continued*

Case No.	Diagnosis	Age	Blood Pressure	Disks			Retinas				Arteries			Veins				Remarks
				Edema	Increased Vascularity	Hemorrhage	Edema	Hemorrhage	Spots	Pigment	Tortuous	Irregular	Arteriosclerosis	Tortuous	Dilatation	Papilledema	Choked Veins	
40	Chronic myocarditis, hypertension	60	182/98	±	+	0	0	0	0	0	+	+++	+++	+	++	+++	0	Definite retinal arteriosclerosis
41	Chronic myocarditis, fibrillation, arteriosclerosis, hypertension	63	184/92	0	0	0	0	+	0	0	+++	+	++	0	+	0	0	Doubtful retinal arteriosclerosis, superficial hemorrhages
42	Chronic myocarditis, auricular fibrillation, hypertension	62	184/100	0	0	0	0	0	0	+	+	+++	++	0	0	+++	0	Definite retinal arteriosclerosis
43	Chronic myocarditis, angina pectoris, hypertension	53	186/98	0	0	0	0	0	0	0	0	+	++	0	0	±	0	Doubtful retinal arteriosclerosis
44	Chronic myocarditis, auricular fibrillation, hypertension	57	194/110	0	0	0	0	0	0	0	+	+++	++	0	+	++	++	Definite retinal arteriosclerosis
45	Chronic myocarditis, arteriosclerosis, hypertension	65	198/120	0	0	0	0	0	0	0	0	+++	+	0	0	+	0	Definite retinal arteriosclerosis, primary type retinal arteriosclerosis
46	Chronic myocarditis, arteriosclerosis, hypertension	52	200/110	0	0	0	0	+	0	0	+++	+++	+++	++	++	+++	++	Definite retinal arteriosclerosis, old superficial and small round hemorrhages
47	Angina pectoris, hypertension, arteriosclerosis	39	206/112	0	0	0	0	+	0	0	0	+++	+++	0	0	++	+	Definite retinal arteriosclerosis, copper wire arteries, small, round hemorrhages
48	Chronic myocarditis, arteriosclerosis, hypertension	57	206/132	+	+	0	0	+++	+	0	++	+++	+++	0	0	+++	0	Definite retinal arteriosclerosis, many small flame shaped, round and irregular hemorrhages, yellowish white spots
49	Chronic myocarditis, arteriosclerosis, hypertension	50	208/110	0	0	0	0	0	±	0	0	+++	++	0	0	++	0	Definite retinal arteriosclerosis, few small gray-white spots
50	Chronic myocarditis, hypertension	72	218/122	0	0	0	0	0	0	0	++	0	++	0	0	++	0	Definite retinal arteriosclerosis
51	Chronic myocarditis, auricular fibrillation, hypertension	59	218/120	0	+	0	0	+	0	0	0	+++	+++	0	0	++	+++	Definite retinal arteriosclerosis, small round hemorrhages
52	Chronic myocarditis, hypertension	51	222/130	0	0	0	0	++	+++	0	+++	++	++	0	0	++	++	Definite retinal arteriosclerosis, small round hemorrhages and gray and white spots
53	Chronic myocarditis, hypertension	55	232/124	0	+	0	0	0	0	0	0	++	+	0	+	++	0	Definite retinal arteriosclerosis
54	Chronic myocarditis, auricular fibrillation, hypertension	71	238/126	0	+	0	0	+	0	0	++	+++	+++	0	+	+++	0	Definite retinal arteriosclerosis, small flame shaped hemorrhages
55	Chronic myocarditis, arteriosclerosis, hypertension	50	242/120	+	..	+	..	+	+	+++	++	++ ++	++ ++	++	0	+	+++	Definite retinal arteriosclerosis, chorioretinitis secondary optic atrophy, small white spots
56	Chronic myocarditis, hypertension	71	275/118	0	0	+	0	0	0	0	++	+	++	0	+	+++	0	Definite retinal arteriosclerosis, small round hemorrhages

56	Chronic myocarditis, hypertension	71	275/118	0	0	+	0	0	0	0	++	+	++	0	+	+++	0	Definite retinal arteriosclerosis, small round hemorrhages
57	Chronic valvular disease, mitral stenosis	18	82/10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
58	Chronic valvular disease, aortic and mitral stenosis and insufficiency	13	102/0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
59	Chronic valvular disease, mitral stenosis auricular fibrillation	29	105/60	0	0	0	0	0	0	0	0	0	0	0	+	0	0	No retinal arteriosclerosis
60	Chronic valvular disease, aortic stenosis and insufficiency	49	112/90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
61	Chronic valvular disease, mitral stenosis	29	112/?	0	0	0	0	0	0	0	0	±	0	0	0	0	0	Doubtful retinal arteriosclerosis
62	Chronic valvular disease, mitral stenosis and insufficiency	23	114/66	0	0	0	0	0	0	0	0	0	+	0	0	0	0	No retinal arteriosclerosis
63	Chronic valvular disease, aortic insufficiency, mitral stenosis and insufficiency	15	118/0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis, pulsation in arteries and veins
64	Chronic valvular disease, mitral stenosis	15	122/60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
65	Chronic valvular disease, mitral stenosis and insufficiency	37	128/80	0	0	0	0	0	0	0	0	0	0	0	0	0	+ +	No retinal arteriosclerosis
66	Chronic valvular disease, mitral stenosis	32	134/60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	No retinal arteriosclerosis
67	Chronic valvular disease, mitral stenosis	45	148/98	0	0	0	0	0	0	0	+ +	+ +	+ +	0	0	±	0	Definite retinal arteriosclerosis
68	Chronic valvular disease, auricular fibrillation	45	148/90	0	0	0	0	0	0	0	+ +	+ +	+ +	0	0	+	0	Definite retinal arteriosclerosis
69	Chronic valvular disease, mitral stenosis and insufficiency	46	150/84	0	0	0	0	0	0	0	0	+ +	0	0	0	+	+ +	Definite retinal arteriosclerosis
70	Chronic valvular disease, mitral stenosis insufficiency, aortic insufficiency	19	150/0	0	0	0	0	0	0	0	+ +	0	+ +	0	0	0	+ + +	Doubtful retinal arteriosclerosis, arteries and veins pulsate, chorioretinitis
71	Chronic valvular disease, aortic insufficiency and stenosis	50	152/78	0	0	0	0	0	0	0	0	+	0	0	0	+	0	Definite retinal arteriosclerosis

patients without hypertension and with a systolic blood pressure of 145 mm. or below and (2) thirty-four patients with hypertension and with a systolic blood pressure above 145 mm. A comparison of the incidence of retinal arteriosclerosis is made in table 10.

SUMMARY OF GROUP VI

An examination of the data reveals that irregularity of lumen and arteriovenous compression are not always present in the same degree. In fourteen cases in which there was marked arteriovenous compressions, ten patients showed definite irregularity of the lumen of the arteries, while in four cases it was only slight or doubtful. In twelve of the foregoing cases, definite changes occurred in the arterial reflex which indicated thickening of the arterial wall, while in contrast definite irregularity of the lumen was observed in seven cases, with slight or no arteriovenous compression. Case 35 is the outstanding example. My impression is that these variations are due largely to the degree of

TABLE 10.—*Retinal Arteriosclerosis in Group VI*

	Definite, Percentage	Doubtful, Percentage	None, Percentage
Without hypertension	68.2	27.3	4.5
With hypertension	91.2	8.8	0.0

intimal change and to the thickening of the media which are present in the individual case, and particularly to the change that predominates.

The most marked pressure effects are usually seen in the cases in which there are thick copper wire arteries; in these cases, the arteries and veins usually cross at right angles. As a result, the compression is clear-cut, and the venous channel is obliterated on each side of the vessel for a distance approximately equal to the central blood column. This, no doubt, corresponds to the thickness of the arterial wall, which is not visible. When by chance the vein crosses the artery, "mounding" of the vein is produced, and the vein forms an inverted loop corresponding to the size of the artery.

Some degree of dilatation of the veins occurred in five of fifty-six cases, and in only one instance in the absence of definite arterial sclerosis. In one case (29), phlebosclerosis was seen. The changes in the veins, with the exception of the compression effects, seem to hold a position of only secondary importance in the recognition of retinal arteriosclerosis.

Some degree of choroid vessel sclerosis was visible with the ophthalmoscope in eighteen of twenty-six cases, and in all but two instances it was associated with definite retinal arteriosclerosis. On the other hand, it was absent in thirty cases in which there was definite retinal arterio-

sclerosis. In this series, it was not as frequent as the studies of Cohen [28] would indicate. It is his opinion that the basic pathologic change in the eyeground is a primary choroidal arteriosclerosis. He considers that the edema of the disks, hemorrhages and spots result wholly from this factor or in combination with some unknown factor. He also states that in many cases sclerosis of the choroidal vessels is more marked than retinal sclerosis, or may be marked when retinal arteriosclerosis is absent.

It would seem, then, from my series, that sclerosis of the choroidal vessels, recognizable with the ophthalmoscope, is rarely observed before retinal arteriosclerosis. It must be taken into account, however, that Cohen's statements are in part based on a study of actual pathologic specimens. Sclerosis of the choroidal vessels in this respect frequently seems to be associated with changes in the disk and the presence of hemorrhages, spots and pigment. Some of these changes were present in thirteen of the eighteen cases of sclerosis of the choroidal vessels and in only thirteen of thirty-eight cases in which such sclerosis was not present. However, in the diabetic group it was a rather frequent occurrence and disk changes were rare. No conclusion can therefore be drawn from my observations.

The changes in the disk and in the retina are not worthy of extended comment. From the table, it may be observed that the incidence is greater in the patients with the higher pressures.

If the group as a whole is considered, the observations suggest that in the majority of cases the myocardial degeneration has probably developed on a basis of previous hypertension (if the assumption that retinal arteriosclerosis is produced by hypertension is correct), and that the patient who has a normal blood pressure at the time of examination has lost his hypertension either prior to, or with the development of, the myocardial insufficiency; and that the degeneration may have been initiated because of general sclerosis of the precapillary vessels, if it is accepted that the condition of the retinal vessels reflects the condition of the small vessels throughout the body. This opinion was first expressed by Gunn,[29] and it has since been reiterated by numerous observers. These observations conform with the clinical observations of Fahr,[30] who is of the opinion that 75 per cent of chronic myocarditis originates on the basis of hypertension.

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28. Cohen, M.: Significance of Pathological Changes in the Fundus, J. A. M. A. **78**:1694 (June 3) 1922.

29. Gunn, Marcus: Tr. Ophth. Soc., London **18**:356, 1898; quoted by Moore (footnote 2).

30. Fahr, G. E.: Hypertension Heart, Most Common Form of So-Called Chronic Myocarditis, J. A. M. A. **80**:981 (April 7) 1923.

The idea of searching for evidence of previous hypertension in the eyegrounds of patients who have chronic myocarditis and whose blood pressure is low or normal was suggested to me by O'Hare. He called to my attention the possible connection between generalized sclerosis of the small vessels and chronic myocarditis. The retinal and clinical aspects of patients with chronic myocarditis will be considered more fully in a future publication.

In one patient under my observation who had definite retinal arteriosclerosis with a blood pressure of 136 systolic and 94 diastolic after rest in bed and digitalis therapy, the blood pressure rose in twenty-four days to 240 systolic and 140 diastolic. Fahr observed a considerable rise in blood pressure in the majority of patients whose condition was diagnosed as myocardial failure while they were in the hospital under treatment.

In comparing the group of patients with chronic valvular disease (table 7) with that in which the patients suffered from chronic myocarditis, an absence of retinal sclerosis is found in ten of fifteen cases. One case shows doubtful, and four cases definite, retinal arteriosclerosis; however, the latter patients had systolic blood pressures over 145 mm. and had reached an age when degenerative changes in the vascular system might become manifest. Changes in the disk and in the retina were absent. Three of four patients with aortic insufficiency showed pulsation both in the arteries and in the veins. Two patients of twelve in this series whose condition was diagnosed as mitral stenosis showed slight hypertension and mitral stenosis. Boas and Fineberg[31] found 29 per cent hypertension in 135 cases of mitral stenosis. Only five of their patients 40 years of age or under had hypertension. The patients in my small series have an average age well below 40, which doubtless accounts for the low incidence of hypertension and retinal arteriosclerosis in mitral stenosis.

SUMMARY

1. A study of twenty cases of thyroid disease with increased basal metabolism shows a rather striking absence of retinal arteriosclerosis when patients in the sixth decade are eliminated.

2. In forty-seven diabetic patients of all ages (excluding children under 12 years) with and without hypertension, the incidence of definite retinal arteriosclerosis was 36.1 per cent in the latter and 81.8 per cent in the former. In both groups considered together, it was 42.5 per cent. These observations indicate that hypertension may play an important rôle in diabetes. The average age of diabetic patients with definite retinal arteriosclerosis was 57.7 years, while in patients showing doubt-

31. Boas, Ernst P., and Meyer H. Fineberg: Hypertension in Its Relationship to Mitral Stenosis and Aortic Insufficiency, Am. J. M. Sc. **172**:648 (Nov.) 1926.

ful or no retinal arteriosclerosis, the average age was 33 years. No patient under 30 years of age showed either definite or doubtful arteriosclerosis. If the presence of retinal arteriosclerosis is an index of sclerosis of the small vessels in other parts of the body (pancreas included), sclerosis of the small vessel may be an important factor in the production of diabetes after 50 years of age.

Likewise, it does not appear to be a factor in the production of diabetes in the young person. Sclerosis of the choroidal vessels is more frequent in diabetes than in the other conditions studied; changes in the disk are infrequent. If the ophthalmologist or internist sees eyegrounds exhibiting abnormally red retinas, numerous small round hemorrhages, groups of small yellowish-white and grayish-white spots on the central field of the retina, arteries with sclerotic changes, an well defined sclerosis of the choroidal vessel in the periphery of the retinal field with normal or nearly normal disks, in a person past middle life, he should strongly suspect diabetes.

3. In a small series of cases of acute and subacute nephritis, retinitis was conspicuous by its absence. The two patients with retinitis both had hypertension.

4. Retinitis occurs with greater frequency in chronic nephritis than in vascular hypertension. Renal retinitis presents certain changes, such as marked papilledema, retinal edema, cotton wool spots and coarse fan and star formation that suggest renal involvement. In retinitis caused by hypertension, these changes are less frequent, but all may occur. Retinitis resulting from hypertension may therefore be indistinguishable from renal retinitis. The change in the eyeground in both instances result from vascular change and diminished blood supply to the retina. It is suggested that such difference in appearance as exists is probably due to the rate at which the degenerative changes occur.

5. A study of the changes in the eyegrounds in fifty-six patients with and without hypertension, in which chronic myocarditis was either the primary or the important secondary diagnosis, revealed the presence of definite retinal arteriosclerosis in 91.2 per cent of the former and in 68.2 per cent of the latter. This observation (if certain criteria previously set forth in this article may be accepted) indicates that previous hypertension may play an important part in the etiology of chronic myocarditis, with and without hypertension.

6. In chronic valvular disease that had developed on a rheumatic basis, retinal arteriosclerosis was absent in two thirds of the cases, and when definite retinal arteriosclerosis was present, it occurred in association with elevation of the blood pressure and in patients who had reached an age when degenerative changes in the vascular system might become manifest.

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ATYPICAL SPRUE

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The diagnosis of sprue is as yet on an unsatisfactory basis. In the late or advanced stages of the disease, clinical recognition is comparatively easy. In its earlier and initial course, it is recognized with considerable difficulty and uncertainty, and diagnosis really rests on its later development into a more or less classic picture. So far as evidence is available, we do not find a close correspondence between the symptoms and the gross pathologic condition. This observation leads to the inference that disturbance of function precedes the establishment of objective cellular changes by a variable and indefinite time. In this respect sprue resembles subacute myelinic degeneration of the spinal cord.

A diagnosis based on the characteristic diarrhea, stomatitis and afebrile course does not include many early cases which later prove to be sprue. Moreover, after this classic picture has been present even for years, one or all of these features may be absent, and the condition may appear as an essential anemia or combined sclerosis. The difficulties are enhanced by ignorance of clearly defined etiology and by an absence of pathognomonic tests. The term "sprue" has loosely covered a rather large and indefinite group of clinical conditions, including the classic picture and cases that grade off in several directions and present only a smattering of one or more of the prominent features of the genuine disease. In the first place, there are the mild but persistent diarrheas, some of which later develop into classic sprue, but in many of which the patients recover without such progression. Physicians see the more characteristic cases which follow or are initiated by dysentery or acute enterocolitis; the cases in which gastric disturbances are the prominent feature, and diarrhea is absent; cases with a history of diarrhea in which the stomatitis and diarrhea have disappeared, but in which the stools are bulky, and the asthenia and loss of weight are progressive; and a group of borderline cases in which the features of sprue are definite, but in which intercurrent clinical and pathologic features are also prominent. Some of these borderline cases are similar to the classic pernicious anemia of Addison's description, and the anemia itself is identical with

the latter. Reference has been made to these mixed or borderline cases in a former article.[1]

The following case reports are further illustrations of this borderline group. Some present evidence of triple system involvement and may be classified as atypical sprue, or perhaps better under a new heading that will indicate the more complex clinicopathologic picture of sprue, pernicious anemia and combined nerve degeneration.

In regard to etiology, the presence of Ashford's *monilia* has been inconstant in these cases, and we are not prepared to accept its pathogenicity as established for sprue itself and even less for these atypical cases. The idea of a gastro-intestinal toxin of a group type, not limited to a single chemical entity, seems now the most logical working hypothesis. The work of Minot,[2] relating to high protein and nuclear diets in pernicious anemia, has been confirmed in our experience, and we have reviewed the dietary treatment of sprue from this standpoint. The suggestion arises naturally that the factor of deficiency in vitamin or protein may have an etiologic bearing on sprue, pernicious anemia and combined degeneration. A later report will be devoted to our own experience along these lines.

CASE REPORTS

CASE 1.—*History.*—J. F. A., a private patient,[3] a man, aged 47, an American, had spent several years in Japan and in travels about the Orient, including China and the Philippines. The previous history included only typhoid and influenza. In Japan, in 1923, he suffered a sudden hard chill, followed by high fever and diarrhea. He did not have dysentery, but he had much colic. Recovery seemed complete in four days. One month later the stools began to be typical of sprue, and stomatitis soon followed. Four months later, when he arrived in San Francisco, examination showed extreme emaciation and a tawny yellow skin. The abdomen was swollen, tympanitic and tender; the liver and spleen were not felt. The Wassermann reaction was negative, and the urine was normal. The stools were negative for blood, parasites and yeasts. The coagulation time of the blood was normal. Examination of the blood showed: red cells, 1,850,000; white cells, 4,100; hemoglobin (Sahli), 36 per cent; polymorphonuclear cells, 48, and lymphocytes, 47. There was great variation in the size and shape of the red cells; the color index was 1.

The blood counts remained similar to this for several months, then gradually returned to normal. Five months after the man arrived in this country, his health was apparently normal, and against advice he returned to Japan. After three months in Japan, his blood count was still normal, and he did not have any symptoms. He then returned to San Francisco in July, 1924. Two days after he landed, stomatitis and stools typical of sprue suddenly developed. Diarrhea, weakness and occasional mild stomatitis were present to some degree during the next two months.

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1. Reed, Alfred C., and Wyckoff, Harry A.: Common Picture of Sprue, Pernicious Anemia and Combined Degeneration, Am. J. Trop. Med. **6**:3 (May) 1926.

2. Minot, G. R.: Treatment of Pernicious Anemia by Special Diet, J. A. M. A. **87**:7 (Aug. 14) 1926.

3. The earlier part of this history has been reported (footnote 1).

After two and a half months in this country, he again, against advice, returned to Japan; he still had some gastro-intestinal disturbance, weakness and a recurrent anemia with a high color index. Three weeks after reaching Japan, he was attacked by intense epidemic intestinal influenza with fever. This gradually led to a recurrence of typical and severe sprue. He began to lose weight. The blood rapidly degenerated to the following picture: red cells, 2,108,000; white cells, 4,600; polymorphonuclear cells, 58 per cent; lymphocytes, 31; mononuclears, 9; hemoglobin (method not given), 47 per cent; color index, 1.12. Numerous nucleated red cells, macrocytes and abnormal shapes were found.

He stayed in Japan for five months. When he reached San Francisco again on April 7, 1925, examinations showed extreme emaciation, yellow, waxy pallor and extreme weakness. He suffered from a constant watery diarrhea. The stools were free from blood, parasites and yeasts. The blood count on April 8 was as follows: red cells, 1,400,000; white cells, 2,325; polymorphonuclear cells, 54 per cent; lymphocytes, 41; eosinophils, 5; hemoglobin (Sahli), 33.2 per cent, and color index, 1.18. Megaloblasts, polychromasia, abnormal shapes and sizes were numerous.

Improvement followed a series of transfusions, until his clinical condition became practically normal in July, 1925, although the blood was still anemic, but the color index was normal. In September, the anemia again advanced and was accompanied by a marked increase of numbness of the hands and feet and by an extreme clumsiness in the motor functions, especially of the hands and feet. Neurologic examination by Dr. Joseph Catton gave the following objective observations: "Definite disturbance in sensation over corresponding areas on outer surface of each foot. In view of the usual findings in cases presenting the blood picture seen in this case, I would be inclined to place the trouble in the cord." There was a steady progression in the anemia, wasting and diarrhea, accompanied by periods of stomatitis. No further symptoms appeared referable to the spinal cord. Transfusions gave only temporary relief. In February, 1926, the clinical picture was that of pernicious anemia, with lemon-hued skin and a typical blood picture of a rather aplastic type.

On March 12, 1926, the blood reached its lowest count, and the patient was in a dying condition, with severe air hunger and cramps in the legs and chest. The blood count was remarkable, as follows: red cells, 835,000; white cells, 5,200; polymorphonuclear cells, 75 per cent; lymphocytes, 23; mononuclears, 2, and hemoglobin (Sahli), 12 per cent. Red cells showed numerous macrocytes and microcytes, the former predominating. Numerous abnormal shapes, some stippling of red cells, occasional normoblasts and a few megaloblasts were present. The actual hemoglobin reading was too low to be entirely accurate.

A new series of transfusions gave temporary respite and comparative comfort for about three months, during which time they alone kept him alive. A total of nineteen transfusions were given during the entire illness. Death occurred on July 3, 1926, in Letterman Hospital, to which the patient was admitted on June 9. During the last month of life, the blood count was maintained fairly well and showed a remarkable "come-back" from the extremely low picture of March 12. On the day before death, the count was as follows: red cells, 2,080,000; white cells, 6,000; hemoglobin (Dare), 55 per cent; polymorphonuclear cells, 62 per cent; lymphocytes, 35; eosinophils, 2, and transitionals, 1. The urine was constantly normal. The results of fractional gastric analysis two weeks before death are shown in table 1.

The degrees of acidity given in table 1 and elsewhere in this article, when not otherwise indicated, are computed on the basis of the amount of tenth normal sodium hydroxide required to neutralize the acid in 100 cc. of filtered gastric contents.

Postmortem Examination.—General examination showed extreme emaciation. The height was 5 feet, 9 inches (175.2 cm.), and the weight was about 110 pounds (49.9 Kg.). The surfaces of the abdomen, arms and legs were covered with

small petechial hemorrhages. There was practically no postmortem lividity. There was no subcutaneous fat, and the musculature was extremely pale, thin and small. The peritoneum was smooth and moist. The appearance of the chest was not remarkable except for a terminal bronchopneumonia. The spleen was small and flabby and weighed 150 Gm.; the cut surface was dark red and studded with numerous small white plaques. The liver weighed 1,125 Gm. and had a dark red and wet cut surface; the capsule was smooth and glistening. Grossly, the gall-bladder was normal. The appearance of the pancreas was not remarkable.

The entire gastro-intestinal tract was dull gray; the mucosa of the sigmoid seemed thickened, while the wall of the small intestine was thin, and the mucosa was almost entirely atrophic. The lower portion of the small intestine was entirely smooth, while the upper portion showed normal folding of the mucosa. The stomach was small and apparently free from pathologic changes.

The suprarenals were small, but seemed normal. The renal pelves were dilated. The glandular and osseous systems were not remarkable.

Sections of the cervicodorsal cord examined by Dr. William Ophüls were normal in appearance.

Pathologic Diagnosis.—The diagnosis was: sprue, bronchopneumonia, anthracosis, reticulo-endothelial hyperplasia of the liver with hemosiderin pigmentation, atrophy and degeneration of the muscle of the heart, hydronephrosis.

Comment.—This case was primarily typical of sprue, with the ordinary early secondary anemia and terminated in the triple system syndrome, which involved

TABLE 1.—*Results of Fractional Gastric Analysis*

Free hydrocholoric acid.....	18	15	26	22	25
Total acid	30	24	50	42	44

the gastro-intestinal tract, the blood and the nervous system. As the sprue developed, and there was a relapse and recurrence, pernicious features developed in the blood until the picture was that of true pernicious anemia, gradually changing into an aplastic type. There were definite and consistent nervous symptoms. In the light of the knowledge of the relation of symptoms to pathologic conditions in subacute degeneration of the spinal cord, this case presents indications of damage to the cord which cannot be ignored. Negative results of postmortem examination of the cord do not change the fact that the cord functioned abnormally in life. A neurologic study of the relation of pathologic conditions to symptoms and of the occurrence of subacute myelinic degeneration in the peripheral nervous system will be published shortly by Joseph Catton, including a neurologic review of several of the cases reported here.

CASE 2.—*History.*—S. W., a man, an American, aged 58, was first seen on July 1, 1926. He had had a severe attack of malaria in 1900, but none since that date and otherwise no noteworthy illnesses had preceded the present one. He was born in England, and went to the eastern part of the United States at the age of 10; in 1898, he went to the Philippines, where he has resided since. His average weight was 130 pounds (59 Kg.), but for the last few years it has been 125 pounds (56.7 Kg.).

The present illness began about three years before presentation with an attack of what was probably bacillary dysentery, for which he was treated and cured by specific serum. From that time he had had constant indigestion, with excessive flatulence, fermentation and occasional looseness of the bowels, but he did not have pain, nausea or vomiting at any time. At times his mouth would become dry, irritated and slightly sore; frequently sour foods would cause pain in the mouth. Starches and sweets aggravated the indigestion. He could eat large quantities of strawberries with ease and improvement. One year before presenta-

tion he had an attack of sore mouth and tongue of moderate severity. He did not use tobacco or alcohol. Anorexia was marked. This status persisted to the time when this article was written with a gradual loss of weight to about 115 pounds (52.1 Kg.) and a gradual decline in strength and energy. He felt that he had become somewhat irascible and irritable. This change in disposition is a rather common feature in ordinary sprue.

Examination.—Examination in July, 1926, showed a slight, rather pale man. Results of a neurologic examination were negative. The mouth was normal; in fact, with the exception of a slightly tympanitic abdomen, he was entirely normal.

Laboratory Observations: gastro-intestinal roentgenograms showed a normal colon. There was an inconclusive suggestion of duodenal ulcer, but it was disproved by further study. The chest was normal, except for scarring of the hilum and the pleura. The Wassermann reaction was negative. The blood calcium was 9.97 mg. Examinations of stools were repeatedly negative for *Protozoa* or other parasites and *Monilia*, except for a few ova of *Trichuris*. A stool examined bacteriologically by Dr. E. C. Dickson showed a predominant gram-negative picture without streptococci or yeasts. Cultures were negative for pathogens. The stools showed an excess of fat. The urine was normal except for the presence of urobilin.

The gastric contents during fasting did not show free acid; the total acid was 10. The first specimen was too small to examine. The second specimen showed a free acid of 15 and a total acid of 35, and the third specimen showed a free acid of 20 and a total acid of 45. The blood count was as follows: red cells, 2,870,000; white cells, 5,150; polymorphonuclears, 63 per cent; lymphocytes, 33; eosinophils, 1; basophils, 2; transitional, 1; reticulated red cells, 1 per cent of the total red cells; hemoglobin (Sahli), 67 per cent; color index, 1.15. No nucleated red cells were seen. Many large, rather faintly staining red cells and moderate poikilocytosis were present.

Treatment and Course.—For two months the only treatment consisted of high purine diet, and the blood count was as follows on October 6: red cells, 2,800,000; white cells, 7,800; hemoglobin (Dare), 62 per cent; color index, 1.1. Antisocytosis was present. The platelets were normal, and there was no stippling.

The diet was then changed to one typical for patients with sprue, containing an abundance of fresh fruits, berries, rare meat and fresh milk, while a restriction was placed on starches and sugar. There was immediate improvement in the digestive condition; the symptoms entirely disappeared, and the appetite returned. During October, a series of four transfusions was given, with iron cacodylate daily by vein. The blood count improved until, on Nov. 23, 1926, it was as follows: red cells, 4,080,000 and hemoglobin (Dare), 82 per cent; the color index was 1.02.

Clinically, the patient is well. His prognosis is probably bad if he returns to the Philippines and good if he remains in this country.

Comment.—This case illustrates the "dysentery" onset of a case of sprue atypical in the absence of characteristic stools, with anemia which had the pernicious features of high color index and increased size of red cells, but which did not yield to a high protein and nuclear diet and which showed almost a specific reaction to a diet for sprue and blood transfusions. The patient did not show subjective or objective evidence of nerve degeneration at any time. It is to be noted that his blood calcium was at a high normal figure, and the contents of the stomach showed a rather low acidity. This is a comparatively early case which may possibly develop into pernicious anemia or in which the typical symptoms of sprue would probably appear if the patient should live in a climate in which the disease was endemic.

CASE 3.—*History.*—(Private.) S. I., a white male, aged 50, had lived in Pennsylvania all of his life until he came to southern California in 1920, except for three months spent in Georgia in 1918. As a child he had had whooping cough, measles and frequent colds and tonsillitis; attacks of tonsillitis did not

disappear until tonsillectomy was performed in 1924. He had not had any other acute diseases. On two occasions he had had mild dysenteric attacks, apparently caused by the consumption of bad food during hot summer weather; otherwise, his gastro-intestinal condition was excellent until this illness. As a young man, he was told that he had a mitral leak, but it never produced symptoms. His average weight in mature life had been 144 pounds (65.2 Kg.). He led an active, normal life; he did not indulge in excesses and did not have any complaints.

His present illness began in December, 1920, when, his general health being normal, he noticed that his mouth was so sore that he could not smoke. This condition was followed by anorexia, indifference to food and indigestion associated with extreme flatulence. The bowel movements were regular, but bulky, pultaceous or mushy. He had increasing asthenia and sleepiness and tired easily. In the following spring, these symptoms became more severe, and paresthesias were noted, especially at the roots of the toes. Each spring for five years, that is, with the onset of hot weather, since coming to California, he had had a recurrence of spruelike symptoms. These attacks had increased in intensity and were accompanied by a gradually increasing anemia, which tended to take on certain pernicious features. In February, 1924, the paresthesias extended to the ulnar distribution of the left hand. During the succeeding summer, he was much run down, lost energy and ambition, was easily exhausted and could not stand exercise. In October, 1924, the paresthesias became much worse. A tonsillectomy was performed. The blood count at that time showed 2,700,000 red cells, 68 per cent hemoglobin and a low white count.

From that time, he gradually lost ground, and the nervous symptoms increased. Gastro-intestinal roentgenograms in October, 1924, showed only quick emptying of the stomach and a spastic colon. There was achylia, with low combined acid in the stomach. Flatulence and fermentation increased. He had several lesions of the skin which were pronounced eczema. A series of injections of iron cacodylate were not beneficial. Intermittent claudication appeared in both legs. Transfusion was performed three times, and the blood count rose to 4,000,000. In January, 1925, it was said that *Giardia* was found, an observation which was not confirmed by us. Thymol was given and resulted in an acute enteritis with fever and severe pain in the right lower quadrant. In the following month he improved, his weight increasing to 148 pounds (67.1 Kg.), and he felt better than he had in several years. This improvement lasted until warm summer weather, when the former symptoms again recurred, and he lost 16 pounds (7.3 Kg.). Exhaustion, stomatitis and flatulence were excessive. Some improvement followed another transfusion in November, 1925.

Examination.—He came under the observation of one of us on Jan. 20, 1926. Physical examination showed a rather poorly developed, asthenic looking man about 50 years of age. The skin was distinctly sallow, but not yellow. The color of the mucous membranes was fairly good. The appearance was definitely not that of pernicious anemia. There was some retraction of the gums and a mild stomatitis. The heart was somewhat enlarged to the left and had a soft systolic apical murmur, also heard at the base. The spleen was easily palpable, the liver not enlarged. The abdomen was tympanitic. Dr. Alderson reported that the patient had a generalized seborrheic dermatitis which he considered secondary to the intestinal condition.

Laboratory tests showed the following blood count: red cells, 2,600,000; white cells, 4,725; polymorphonuclears, 45 per cent; lymphocytes, 36; hemoglobin (Sahli), 60 per cent; mononuclear and transitional cells, 10 per cent; eosinophils, 7; basophils, 2; color index, 1.15.

There were no nucleated cells. Moderate poikilocytosis, an occasional macrocyte with diffuse bluing and many small red cells were present. The polymorphonuclear white cells had an increased amount of lobulation, some showing seven lobes.

The Wassermann reaction was negative. The blood calcium was 8.65 mg. per hundred cubic centimeters. On the following day the blood calcium was 9.812 mg., and the blood count showed: red cells, 2,227,000; white cells, 4,200; polymorphonuclears, 48 per cent; lymphocytes, 43; eosinophils, 7; basophils, 1; transitionals, 1; hemoglobin (Sahli), 66 per cent, and a color index of 1.5.

No parasites were found on repeated, adequate examinations of the stools. Specimens contained bile pigment and increased amount of fat, but no blood. Smears showed no cells, but Dr. E. C. Dickson found many bacteria, including long chains of streptococci, many gram-positive cocci and many gram-positive bacilli. Cultures showed a mixed growth of hemolytic and nonhemolytic streptococci, *Staphylococcus albus* and a mucinous-appearing gram-negative bacillus. No growth was obtained of dysentery bacilli, *B. welchii* or *oidia*. Inoculations of rabbits were also negative for these organisms.

The urine was constantly normal. The temperature while the patient was under observation ranged between 97.4 F. and 99.4 F. The pulse and respiration rates were normal.

Studies of the gastro-intestinal tract by roentgenograms with those taken after a barium enema, were made by Dr. R. R. Newell, and did not show any abnormality.

Examination of the contents of the stomach gave the results shown in table 2.

TABLE 2.—*Acidity as Shown by Contents of Stomach*

	Free HCL	Total acidity
Fasting	0	10
Specimen I	0	5
Specimen II	0	5
Specimen III	0	10
Specimen IV	0	Not sufficient quantity

There was no lactic acid or occult blood, but much mucus.

Dr. Joseph Catton summarized the neurologic examination as follows. A physiologic functional change was present, which was capable of more or less complete restoration to normal if the non-neurologic phases of the case were improved or cured. The physiologic function of the spinal cord had been disturbed by toxins, but its structure was intact. Definite subacute degeneration of the posterolateral tracts of the spinal cord had taken place. There had been paresthesias of all four extremities, commencing with the fingers and toes and later involving the legs. On one occasion while playing cards on a train his left arm rested on a window ledge in such a manner that there may have been some exposure to draft and trauma. Following this, there were extensive paresthesias in the left ulnar distribution, which were similar to paresthesias that occurred later in his illness without trauma or exposure. There were no symptoms referable to the cranial nerves. The only motor symptom, in addition to generalized weakness, was an increase in the muscle tone of the lower extremities following extensive exercise. The organic reflexes and the autonomic nervous system were undisturbed. Abnormal psychotic elements were not present. The cranial nerves were normal. The finger-tips showed a diminution of touch, pain and temperature sensations. These sensations were also delayed and were accompanied by paresthesias. The same phenomena were found on the tips and plantar surfaces of the great toes. There was a small spot over the inner side of the left ankle in which touch, pain, temperature and vibratory senses were impaired. Stereognosis was normal. There was a slight disturbance in balance when the patient stood on one foot with eyes closed. The upper tendon reflexes were within normal and were a little greater on the left side. Patellar reflexes were increased, with no ankle clonus. There were no pathologic signs in the great toe.

Dr. H. Y. McNaught, who examined the nose and throat, reported a low grade ethmoid infection of secondary importance which was to be attacked directly only if there was no other line of effective treatment.

Duodenal drainage by the Lyons-Meltzer method for the bile system did not show any cells, but many bacteria, including long chains of streptococci, many gram-positive cocci in pairs, singly and in clusters and many gram-positive bacilli. Cultures showed a mixed growth of hemolytic and nonhemolytic streptococci, *Staphylococcus albus* and a mucinous-appearing gram-positive bacillus seen also in stools. These studies were made by Dr. E. C. Dickson, who felt that in spite of the low acidity of the stomach, the streptococcal content of the bile was above normal. It is to be noted that the finding of *Giardia* was reported in an earlier examination elsewhere, but this organism was not found by us.

Progress of Case.—In spite of a rather unfavorable regimen of work, the patient's energy and weight had improved on March 12, 1926, and there had been only a few episodes of fermentative, loose stools. The sensory disturbances, which were subject to a wide diurnal variation, had abated considerably. The first to appear, the greatest in intensity and the last to recede were in the distal portions of the extremities. Undoubtedly a large share of this damage was peripheral.

On April 14, 1926, the blood count was: red cells, 3,670,000; white cells, 6,200; polymorphonuclears, 64 per cent; lymphocytes, 36; hemoglobin, 75 per cent; color index, 1.04; poikilocytes, a few; macrocytes, very few; microcytes, a few. The patient's weight had increased 10 pounds (4.5 Kg.), and strength, energy and endurance were much improved. He had been on a classic diet for patients with sprue which had a high purine content. Hydrochloric acid was given in large doses with meals and pancreatic extract with bile salts. Occasional courses of castor oil were used, and for the fermentation periods, a mixture of tannalbin, kaolin and thymol.

Case 4.—*History.*—A. J. M., a white man, aged, 59, with a clinical diagnosis of transverse myelitis, had lived in the Philippines from 1904 to 1917, during which time he had suffered a mild attack of dysentery of undetermined type. He had typhoid at 21 years of age.

The history of his illness was evidently incomplete. He was under observation only one week, and while he was said to have been in good health until January, 1926, the pathologic condition at death was scarcely compatible with so short an illness. His illness was said to date from an attack of influenza in January, 1926, when he developed diarrhea which persisted to the end. The stools were foamy, foul and copious; from four to eight a day. He failed rapidly and lost from 40 to 50 pounds (18.1 to 22.7 Kg.) in weight. There was no history of nausea, vomiting or abdominal pain, but he had a sore mouth for the last three months of his life, and a constant mild indigestion. He was bedfast for the last three weeks.

Examination.—Physical examination revealed that he was physically helpless and emaciated, with a mild icteric tinge. There was marked pyorrhea, gingivitis, sordes and a number of carious teeth. The liver was palpable on deep inspiration and slightly tender. The spleen was not palpable. Neurologic examination revealed "marked combined sclerosis." The blood count was as follows on June 18: red cells, 2,500,000; white cells, 6,800; hemoglobin, 50 per cent.

On June 21, a transfusion of 500 cc. of blood was given. On that day the platelets were 83,600; and with hypotonic sodium chloride solutions hemolysis began in 0.32 per cent and was complete in 0.26 per cent.

The contents of the stomach showed absence of free hydrochloric acid during fasting and in the two fractional specimens examined. The total acidity was 12, 6 and 4, respectively.

The urine was normal. Examinations were not made of the stools or spinal fluid. A Wassermann test was not made. The patient died on June 23.

Autopsy.—Autopsy showed an advanced degeneration of the lateral and posterior columns of the spinal cord, chronic cerebral leptomeningitis, pulmonary edema and

some hemosiderin in the liver cells. No pathologic condition was noted in the gastro-intestinal tract except that the small intestine contained mucus, and the colon was distended with foul-smelling, slate-colored material.

CASE 5—*History.*—G. B., aged 55, colored, who had lived in the Philippines for eighteen years, had been in a hospital in 1901 with "sour stomach" and diarrhea. In 1903, he had been operated on for ventral hernia. The definite history of his illness dated from June, 1923, when he had a painless diarrhea with sore mouth, which persisted. In 1924 he had entered a hospital in the Philippines with "marked anemia." The record of the blood picture in that illness was not available. A roentgenogram at that time demonstrated a constriction in the descending colon and intra-abdominal adhesions. Improvement was temporary, and he was sent to the United States in August of that year. He was much emaciated and particularly dehydrated.

Examination.—The blood pressure was: 105, systolic, and 60, diastolic; general abdominal tenderness was present. The liver and spleen were not palpable, and the nervous system was reported normal. The mouth and esophagus were extremely sore. Bulky stools showed faulty digestion of fat; the gastric contents were usually achylic. The peripheral arteries were hard.

Laboratory examination gave the following results:

The Wassermann reaction was negative, and the urine was normal. A blood count on April 22, 1924, showed: red cells, 2,100,000; hemoglobin, 60 per cent; white cells, 6,000. There was marked anisocytosis and poikilocytosis, and many macrocytes and microsytes. The stools showed many fatty acid crystals and globules of fat. The cultures were negative for *Monilia.*

On Aug. 3, 1924, the blood count was: red cells, 1,840,000; hemoglobin (Dare), 35 per cent; white cells, 5,800. There was marked polychromatophilia.

The contents of the stomach in fasting did not show any free hydrocholoric acid and the total acid was 2.

Treatment and Course.—The patient was placed on a liberal diet of fruit and vegetables, and while there was some lessening of pain, diarrhea persisted, and he had fever at times. He later gained about 17 pounds (7.7 Kg.) on a diet of oatmeal and soup. This improvement was temporary, and he was finally reduced to a milk diet, in spite of which diarrhea continued. The blood transfusions failed to influence the blood picture. He died on Oct. 18, 1924. Autopsy was not performed.

CASE 6.—*History.*—C. L. W., a white soldier, aged 42, who had had nine years' service in the Philippines in three-year periods during the past seventeen years, had contracted malaria there in 1908, hookworm in 1912 and dysentery, probably bacillary, in 1917. He had been a steady user of alcohol and tobacco to excess. He was distinctly below par mentally, and a clear history of onset of the illness was not obtained. It is likely that he had had intermittent intestinal disturbance since the attack of dysentery in 1917, but it was not until January, 1925, that his commanding officer noticed that he was weak and obviously ill, and he was sent to the hospital in Manila. He had lost about 40 pounds (18.1 Kg.) in weight, but he did not have pain and did not vomit or cough. In a few days he was transferred to the United States. It was noted that he had from three to four stools a day, tan colored at times, smooth, semisolid and free from gas; at other times they were liquid, yellow, foamy and contained some mucus. His only other symptoms were weakness and a daily afternoon rise of temperature.

Examination.—Physical examination revealed pigmentation of the skin on the exposed parts and evidence of dehydration in dryness and loss of elasticity. The mucosae were pale and muddy. There was marked pyorrhea; the tongue was coated white, with beefy red margins.

The blood count showed: red cells, 2,750,000; hemoglobin, 65 per cent; white cells, 11,400; polymorphonuclear, 82 per cent. Microcytes and poikilocytes were noted.

A tentative diagnosis of sprue was made, and calcium lactate was prescribed and later parathyroid extract and a diet of boiled milk and bananas. In spite of his indifference in following the diet, there was considerable improvement after a month. The stools became formed, he gained in weight and strength, and there was a lowering of the afternoon temperature.

Treatment and Course.—A transfusion was performed shortly after he was admitted, and his blood picture improved considerably, the red cells increasing to 4,940,000 and the hemoglobin to 80 per cent. This was only temporary, however, for the hemoglobin dropped to 65 per cent a few days later.

It was soon discovered by physical signs, roentgenograms and positive sputum that he had an active pulmonary tuberculosis, and he was transferred to Denver In the meantime, it was found that he had achlorhydria, and *Monilia psilosis* was isolated from his stools and from scrapings from his tongue. Neurologic examination was negative for changes in the cord.

The patient's subsequent history and the present status of his case is not known, for he left the hospital in Denver in December, 1925, after a few months of observation.

Case 7.—*History.*—C. C. S., a white man, aged 50, who had lived thirteen years in the Philippines before being invalided home in June, 1926, had a definite alcoholic history. He had malaria in 1900, but there was no history of dysentery. The illness began rather suddenly in April, 1926, with sore mouth and diarrhea. He had five or six yellow, foamy stools during the day and as many at night. There was considerable asthenia, and his mouth was so sore that he was restricted to liquid diet. He entered a hospital in Manila, where a diagnosis of sprue was made. He received twenty doses of emetin, though there is no record of an amebic infection having been demonstrated. He was also given a course of treatment with calcium lactate and parathyroid. He had never had jaundice, but he had had some edema of the feet for two years prior to examination. He was 10 pounds (4.5 Kg.) underweight when he arrived in San Francisco; his tongue was glazed and swollen, with a few abrasions along the edges. The blood pressure was systolic, 100, and diastolic, 64. The abdomen was relaxed, the spleen was not felt, but there was slight tenderness over the gallbladder and the right kidney and considerable gas in the lower bowel. The cutaneous reflexes were exaggerated, and the muscles were hyperactive.

There was some improvement after he returned to the United States; the stools were firmer and fewer; edema of the feet disappeared, and the condition of the tongue improved, though it remained glazed and red. After a more liberal diet, diarrhea returned, and it was necessary again to restrict the patient to fresh fruits and vegetables. The lactate and parathyroid were continued, and he improved sufficiently to leave the hospital on Aug. 25, 1926. Since then we have not heard from him.

Laboratory Observations.—The stools did not show mucus, blood or parasites on several examinations. On June 7, 1926, the blood count showed: red cells, 2,850,000; hemoglobin, 55 per cent (Dare); white cells, 5,200, and polymorphonuclears, 56 per cent. On June 14, it was: red cells, 2,100,000; hemoglobin, 50 per cent; white cells, 7,400; platelets, 165,400. The van den Bergh test gave negative results.

On July 5, the blood count was: red cells, 2,400,000; hemoglobin, 60 per cent; reticulated cells, 1 per cent. The Wassermann reaction was negative.

The contents of the stomach did not show free hydrocholoric acid during fasting; fractional specimens did not show free hydrochloric acid in the first three, 16 and 11 in the fourth and fifth, respectively. The total acidity varied from 11 to 38 cc.

A culture from the tongue was negative for *Monilia.*

CASE 8.—*History.*—J. J. O'B., a white man, aged 56, who had served six and a half years in the Philippines, where he had amebic dysentery in 1900 to 1901, had been a heavy drinker until 1912, but had been temperate since then. He said that he had had good health generally until 1922, when he began to vomit after meals and to have diarrhea. He lost 36 pounds (16.3 Kg.) in weight in a few months. He was hospitalized for more than a year, during which time he was on a diet low in carbohydrates and fats, and he gained 40 pounds (18.1 Kg.). During this admission, it was noted that his tongue was bright red and smooth; the deep reflexes increased; acids in the stomach were reduced; the blood pressure was 80 systolic and 60 diastolic, and he was anemic. He was discharged in August, 1923, but soon regressed on improper diet, returned to the hospital and stayed until October, 1924. He regained lost weight and was having one solid stool a day when he left. From November, 1924, however, he had been steadily losing in weight and strength. He had an average of ten watery, yellowish, foamy, bubbling, copious stools a day; he had lost his appetite, and when diarrhea was worst, his tongue was sore. He came under observation again in March, 1926, when he had lost 30 pounds (13.6 Kg.) in weight and was anemic. The blood pressure was: 90 systolic, and 70 diastolic, and the arteries were markedly sclerosed. He did not respond to treatment, and one transfusion made no impression on the blood picture. His stools were examined many times during the four years of observation and were invariably negative for parasites and *Monilia*, but there was usually evidence of poor digestion of fat. Several roentgenograms of the gastro-intestinal tract failed to reveal any pathologic condition. The Wassermann reaction was negative. At no time during this period was there any fever. For a period of about eight months, beginning in June, 1923, he suffered from neuritis involving both brachial plexuses. During the four years, his condition was variously diagnosed pernicious anemia, gastric ulcer, chronic dysentery and finally sprue.

The first blood picture on record is dated April 13, 1922. It is obvious that the anemia antedates this, and it is a question whether it was not well established when the gastro-intestinal symptoms appeared. The following is a chronologic record of the examinations of his blood.

On April 13, 1922, the count was: red cells, 2,760,000; hemoglobin, 60 per cent. Considerable poikilocytosis was noted, and "platelets diminished."

On May 25, 1922, the blood showed: red cells, 1,820,000; hemoglobin, 60 per cent; marked anisocytosis and poikilocytosis, but no nucleated red cells; white cells, 2,800; polymorphonuclears, 28 per cent. In July, 1922, it showed: red cells, 3,460,000; hemoglobin, 75 per cent; in October, 1922: red cells, 4,510,000; hemoglobin, 80 per cent; in December, 1924: red cells, 3,100,000; hemoglobin, 65 per cent, and in April, 1926: red cells, 2,140,000; hemoglobin, 70 per cent. At this time he had an icterus index of 6.9 and a positive indirect Van den Bergh reaction.

In June, 1926, the count was: red cells, 2,600,000; hemoglobin, 65 per cent; in September, 1926: red cells, 1,150,000; hemoglobin, 40 per cent; in November, 1926: red cells, 1,050,000; hemoglobin, 20 per cent, and in December, 1926: red cells, 870,000; hemoglobin, ?.

He died on Jan. 14, 1927, and the pertinent autopsy observations were as follows: The body was extremely emaciated and there were numerous petechiae on the dorsal surfaces of both hands. All intra-abdominal lymph nodes were moderately enlarged. The mucosa of the small intestine was moderately congested, but otherwise not remarkable. Lymph elements could not be distinguished in the ilium. The mucosa of the colon was perfectly smooth, the wall thin and anemic. The spleen was small. The bone marrow was pure yellow, and histologically it did not show any attempt at hemopoiesis. There was considerable hemosiderin in the liver cells. Bronchopneumonia was the immediate cause of death. The central nervous system was not examined.

SUMMARY

The pertinent features of the eight cases described are more clearly presented in the following summary:

1. Personal History—(*a*) Tropical residence 7
   (*b*) Sex, males 8
   (*c*) Age, 42-47, 2; 50-59..... 6
   (*d*) History of dysentery..... 3
   (*e*) History of alcohol..... 3
2. Onset—(*a*) Diarrhea 5
   (*b*) Sore mouth 1
   (*c*) Indigestion 2
3. Symptom Distribution—(*a*) Sore mouth 8
   (*b*) Achlorhydria 7
   (*c*) Diarrhea 8
   (*d*) Anemia 8
   Remittent 5
   Progressive 3
   (*e*) Central nerve symptoms..... 3
   (*f*) Peripheral nerve symptoms..... 2
4. Predominant Complex—(*a*) Gastro-intestinal, anemia and nervous..... 3
   (*b*) Gastro-intestinal and anemia 4
   (*c*) Gastro-intestinal 1
5. Duration in 4 patients who died—No. 1, 3 years.
   No. 4, 6 months.
   No. 5, 1½ years.
   No. 8, 4½ years.
   Duration in 4 patients still living—No. 2, 4 years.
   No. 3, 6 years.
   No. 6, 8 years.
   No. 7, 4 months.

The whole group showed sore mouth and diarrhea as prominent features, though these symptoms were more or less remittent, and, while diarrhea usually occurred first, sore mouth usually developed early and was more or less synchronous with diarrheal episodes. A definite anemia of pernicious type was seen in all, but it was impossible to place it in relation to the onset. This is a feature the patient could not determine himself, and it was usually not discovered until he had come under competent observation, but as it was usually well advanced, even in the cases seen shortly after onset of the obvious symptoms of the digestive tract, it is reasonable to assume that the "toxin" begins its attack on the blood in most cases early in the disease.

Seven of the cases showed a definite achlorhydria, the other one showed approximately 50 per cent reduction, and the majority showed evidence of pancreatic deficiency in the stools. This breakdown of the digestive function, in fact, is the most constant and striking feature of the disease. The fact that a number of patients give a history of "dysentery" may be significant, but it may as well be incidental in those cases

in which the diagnosis of dysentery is accurate. When the dysenteric diagnosis is not accurate, it may indicate, as does the digestive dysfunction, the onset of sprue and that the alimentary tract bears the brunt of the initial attack of the causative agents.

Sprue is preeminently a disease of white people in a tropical environment, in spite of exceptions to the contrary. The fact that in this group all the patients were men does not mean, of course, that the disease is confined to the male sex. We have seen several cases in women, but the data in their cases are not complete enough to include them. There is no doubt, however, that the disease occurs more commonly in men, perhaps because of their greater likelihood of contact with the etiologic factors. It is certainly a disease of adult life; not that clinical sprue does not occur in children, but the latter seem to be able to "come back" more completely and permanently under proper environment and are not so liable to the pernicious complex we are discussing.

The data presented would form little or no basis for a discussion of the etiology of the condition, and this will not be attempted; our idea is expressed simply as a hazardous conclusion.

One of us, during a three-year tour of duty in the Philippines, came in contact with a group of eleven cases which can be presented as a composite picture rather than individual cases partly because they were so similar and partly because in some instances the data are not sufficiently complete to warrant separate case reports. This group includes Americans and Englishmen and Spanish and Chinese mestizos, all with a long tropical residence, nine of them men, two women, and all well beyond middle age. They were seen in well advanced stages of anemia, and all died within a period varying from a few days to several months after coming under observation. The anemia was invariably aplastic in type and progressive in spite of all treatment. They all suffered from the digestive disturbances incident to achlorhydria, and they all gave a history of a previous intestinal phase in which they had suffered from persistent or sporadic diarrhea of from several months' to several years' duration, a feature that had usually been diagnosed chronic dysentery. In several of the cases, however, this condition persisted to the end, and we were able to study the character of the stools. They were the large, bulky, fermentative, foul discharges considered characteristic of sprue, free from any cellular or pathogenic content. In only one case was *Monilia* isolated, and then it was isolated from the blood by Dr. Smith, then professor of pathology in the medical school of the University of the Philippines. As a rule, however, the intestinal element had largely disappeared from the picture when the patients came under our observation, and the condition was being handled as anemia. It is not possible to speak of involvement of the nervous system in the cases, for the

patients were usually bedridden from asthenia when seen, and the previous history was not always reliable in regard to the subtle symptoms that indicate such involvement.

CONCLUSIONS

1. There is a definite clinical entity, combining gastro-intestinal disturbances like those of sprue, an anemia approaching the so-called pernicious primary type and nervous phenomena characteristic of subacute myelinic degeneration of the spinal cord and of the peripheral nerves. Any combination of these groups may be found associated. We have described eight such cases under the heading of atypical sprue.

2. This variety of atypical sprue occurs chiefly in white men resident for varying periods in tropical or subtropical climates. This fact may account for the predominance of gastro-intestinal symptoms, in which it differs from Addisonian anemia. It is progressive, and, although remissions occur, the course usually proceeds to a fatal termination.

3. If it is assumed that these borderline or composite cases with polysystemic damage are the result of a single type of toxin of gastro-intestinal origin, it seems reasonable to suppose that classic sprue, Addisonian anemia or myelinic degeneration may have a similar etiology, and at times develop into this pleomorphic picture.

SERUM BILIRUBIN IN HEALTH AND IN DISEASE *

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In recent years, interest in jaundice has been largely transferred from the color of the skin and the presence or absence of bile pigment in the urine and feces to the changes occurring in the blood serum, much in the same way that physicians have become concerned with the urea content of the blood in nephritis, and with the concentration of blood sugar in cases of diabetes mellitus. The introduction of new and more delicate methods for the detection and estimation of bilirubin in the serum is responsible for this change in point of view. Perhaps the most notable method has been that of Hijmans van den Bergh of Utrecht, Holland,[1] popularized among the English speaking peoples by the publications of McNee of the University College of London.[2]

Estimations of serum bilirubin are necessary for the detection of potential or latent and also of transient states of jaundice, for the bilirubin content of the blood must reach a certain concentration before bilirubinuria [3] occurs, and contact with the tissues must take place for a period of time before they assume a yellow color (Frerichs,[4] van den Bergh [5]). Transient jaundice, unaccompanied by bilirubinuria or icterus of the tissues, occurs in attacks of gallstone colic (Meulengracht,[6] van den Bergh [5]). Latent states of jaundice are present in patients receiving arsphenamine (Gerrard [7]) and frequently in pernicious anemia

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1. Van den Bergh, A. A. Hijmans: Der Gallenfarbstoff Im Blute, Leyden, 1918. Van den Bergh, A. A. Hijmans, and Snapper, J.: Deutsches Arch. f. klin. Med. **110**:540, 1913. Van den Bergh, A. A. Hijmans: Presse méd. **29**:441, 1921.

2. McNee, J. W.: Brit. M. J. **1**:716, 1922; Quart. J. Med. **16**:390, 1923. McNee, J. W., and Keefer, C. S.: Brit. M. J. **2**:52, 1925.

3. Van den Bergh (footnote 1, reference 1) has found this level (renal threshhold) to be 2 mg. in cases of obstructive jaundice. This has been substantiated by a number of authors (McNee) and is confirmed in this study. Andrewes found it to be usually around 1.75 mg. The kidneys are apparently impermeable to the bilirubin, giving only an indirect reaction (Andrewes: Quart. J. Med. **18**:19, 1924).

4. Frerichs, F. T.: A Clinical Treatise on Diseases of the Liver, trans. by Murchison, C. **1**:66, 1879.

5. Van den Bergh (footnote 1, reference 1).

6. Meulengracht, E.: Demonstration of Transient Jaundice in Gallstone Colic, Arch. Int. Med. **35**:214 (Feb.) 1925.

7. Gerrard, W. I.: Brit. M. J. **1**:224, 1924.

(van den Bergh,[5] Lepehne[8] et al.), and in malignant metastases to the liver (Greene et al.[9]). Once the tissues become stained with the bile pigment (van den Bergh[5]), which they hold for a definite period of time, it follows that their color may not always be a true index of the degree of jaundice present, in contrast to the level of serum bilirubin. Determinations of the bilirubin content of the blood help to distinguish yellowish discolorations of the skin due to it from those due to other pigments, e. g., carotin or lutein. By means of the van den Bergh technic, increases in serum bilirubin due to "obstructive" lesions which give prompt or direct reactions are differentiated from those occurring in "hemolytic" diseases, which give delayed or indirect reactions (Lepehne,[8] McNee[10] et al.). Lastly, the amount of bile pigment present in the blood may afford some idea, especially when it is abnormally increased, of the functional integrity of the liver, in the light of the recent work of Mann and his associates,[11] according to which bilirubin is formed chiefly in the bone marrow and spleen and is apparently primarily excreted, though formed to a slight extent, by the liver. It has been found that some parallelism exists between the degree of bilirubinemia and the retention of dyes of the halogen-phthalein series known to be excreted by the liver (Snell et al.[12]).

The bile pigment content of the blood in the following study was estimated by the van den Bergh method, the original technic being employed[13] in cases showing a delayed (more than one minute) or indirect reaction; the principle of Thannhauser and Andersen[14] was employed in cases showing a prompt reaction,[15] the original iron rhodondate solution of van den Bergh being employed as a quantitative

8. Lepehne, G.: Deutsches Arch. f. klin. Med. **132**:96, 1920; **135**:79, 1921.

9. Greene, C. H.; McVicar, C. S.; Walters, W., and Rowntree, L. G.: Diseases of Liver, Arch. Int. Med. **36**:542 (Oct.) 1925.

10. McNee (footnote 2, second reference).

11. Mann, F. C.; Bollman, J. L., and Magath, T. B.: Am. J. Physiol. **69**:393, 1924. Mann, F. C.; Sheard, C. H., and Bollman, J. L.: Ibid. **74**:49, 1925. Mann, F. C.; Sheard, C. H.; Bollman, J. L., and Baldes, E. J.: Ibid. **74**:497, 1925; **76**:306, 1926; **77**:219, 1926.

12. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of Liver, Arch. Int. Med. **36**:273 (Aug.) 1925.

13. The qualitative and quantitative technic in which only a delayed or indirect reaction is obtained is given by McNee (footnote 2, second reference) or Ravdin (Am. J. M. Sc. **169**:850, 1925).

14. Thannhauser, J. S., and Andersen, E.: Deutsches Arch. f. klin. Med. **137**: 179, 1921.

15. The method consists of 1 cc. of serum + 0.5 cc. of diazo reagent + (after five minutes) 1 cc. saturated solution of ammonium sulphate + 5 cc. of alcohol (96 per cent). This is centrifugalized at high speed. The supernatant liquid is read against the standard. The dilution factor is 7.5. Greene (personal communication to the author) uses double the quantity of ingredients, 2 cc. of serum + 1 cc. of reagent, etc.

standard. That no difference in the quantitative readings in cases showing only an indirect or delayed reaction occurs whether van den Bergh's original method or that of Thannhauser and Andersen is used was noted by the last named and was also determined in this study. The readings are designated in milligrams per hundred cubic centimeters of serum, as others have done, instead of the unit or 1 in 200,000 parts of serum originally designated by van den Bergh, 0.5 mg. per hundred cubic centimeters being the equivalent of 1 unit. As some difficulty was experienced in making readings of less than 0.2 mg. per cent, these are all designated as —0.2 mg. per cent. As it has been found, as was emphasized by Lepehne,[8] that serum bilirubin tends to diminish on standing, because of oxidation to biliverdin, estimations were made within from one to two hours after the blood was obtained. Specimens kept in the dark and on ice show practically no diminution over night. No differences in the readings were noted whether plasma or serum was used, as others have experienced.[16]

Biphasic reactions described by Feigl and Querner[17] have been included under the direct reactions for reasons similar to those of Andrewes (McNee and Keefer[2]). It is felt that they represent quantitative transitions between the indirect and the direct reactions, having been encountered early in experimental ligation of the common duct and late in cases of catarrhal jaundice in the course of this study. Greene also does not consider such a reaction separately.[18]

NORMAL SERUM BILIRUBIN

The van den Bergh reaction was applied to the blood of 202 "normals" of the following age groups:

From 5 months to 9 years	11
From 10 to 19 years	11
From 20 to 29 years	101
From 30 to 39 years	28
From 40 to 49 years	24
From 50 to 59 years	20
From 60 to 69 years	7

The group of normals was composed of 112 medical students, interns and nurses in good health (most of whom had had a recent physical examination); twenty-six individuals above 30 years of age found to be normal at the Pay-Health Clinic conducted under the auspices of The United Jewish Social Agencies; forty-six inmates of

16. McNee (footnote 2, second reference). Ravdin, E. G.: Am. J. M. Sc. **169**:850, 1925.

17. Feigl, J., and Querner, E.: Ztschr. f. d. ges. exper. Med. **9**:153, 1919.

18. Greene, C. H.: Personal communication to the author.

Longview Hospital for the Insane (twenty-seven males, nineteen females), normal physically but affected with a psychosis other than alcoholic; twelve children, five in the pediatric service of the Cincinnati General Hospital for gonorrheal vaginitis, five at the Branch Hospital for Tuberculosis on account of a "contact history," and two examined in private life; and six relatives of the four individuals giving the highest values.

In 193, or 95.54 per cent of the normals, the value of serum bilirubin was less than 0.6 mg.; in six, or 2.97 per cent, it was between 0.6 and 0.9 mg., and in three, or 1.49 per cent, between 1.0 and 1.5 mg. The relative values in the two sexes and the total percentage frequency of any given value or less are illustrated in table 1.

This table would indicate that the level of serum bilirubin is relatively higher in males than in females, for in thirty, or 47 per cent, of

TABLE 1.—*Relative Values and Total Percentage Frequency of Any Given Value or Less*

Mg. Bilirubin*	Per Cent Males	Per Cent Females	Total per Cent Having Given Value or Less
—0.2	28.2	47.0	34.15
0.2–0.29	30.4	26.5	63.36
0.3–0.39	19.0	14.0	80.69
0.4–0.49	8.7	8.0	89.1
0.5–0.59	8.7	1.5	95.54
0.6–0.69	0.0	1.5	96.03
0.7–0.79	2.1	1.5	98.01
0.8–0.89	0.72	0.0	98.51
0.9–0.99	0.0	0.0	.....
1.0–1.5	2.1	0.0	100.0

* Blood taken from one to four hours after a meal. The value of milligrams of bilirubin denotes the amount per hundred cubic centimeters of serum. The reactions were all indirect.

the females, the bilirubin value was less than 0.2 mg. in contrast to thirty-eight or 28.2 per cent of the males, and in three females, or 4.5 per cent, above 0.5 mg., in contrast to nineteen males, or 13.6 per cent above this level. The four values above 0.8 mg. were limited to the males. No distinct differences were observed in the various age groups. The blood from the umbilical cord of thirteen new-born infants was examined in addition, and the physiologic hyperbilirubinemia described by van den Bergh and others was encountered, the readings being in the vicinity of 1 mg. or more.

That the value of the serum bilirubin is not absolutely constant was first shown by Gilbert and Herscher,[19] who found it to increase somewhat during fasting. The blood of three of the normal individuals here studied was examined daily before breakfast for one week, a maximum variation of 0.2 mg. being noted. Förster and Förstner,[20] who exam-

19. Gilbert and Herscher: Presse méd., 1906, no. *27*; quoted by van den Bergh.

20. Förster, J., and Förstner, B.: Ztschr. f. klin. Med. **103**:703, 1926.

ined eighteen individuals with various diseases under the foregoing conditions, employing the technic of Ernst and Förster,[21] found a variation generally between 0.1 and 0.3 mg. On examining twenty-one individuals before breakfast, two hours after the noon meal, and before the evening meal, they found the highest values generally, but not always, before breakfast. The fluctuations were generally from 0.1 to 0.2 mg. Broun et al.[22] found a variation of as high as 0.5 mg. in a normal individual, the blood being taken before breakfast, before dinner (12:00) and at 4:00 p. m. According to Meyer and Knüpffer,[23] the blood bilirubin diminishes in quantity from two to five hours after meals, and increases after eight hours, apparently on the basis that during digestion bilirubin is excreted from the blood (Förster and Förstner).

As 98 per cent of the normal patients had a value of approximately 0.8 mg. or less, 1 mg. may be safely considered the upper limit of normal, thus allowing 0.2 mg. for fluctuation during the day and from day to day. As a value of 0.6 and 1 mg. was exceeded in only 4.5 per cent of the cases, any value between 0.6 and 1 mg. should be considered as possibly indicative of an increase, particularly as the latter figure is approached. In his monograph, van den Bergh[24] states that in the vast majority of healthy individuals the values found are between 0.25 and 0.4 mg. (from 1 to 400,000 to 1 to 250,000). In a later paper published in France,[25] he gives figures for the bilirubin content of normal human serum of from 0.1 mg. to 0.25 mg. (1:1,000,000 to 1:400,000), which have been accepted by Lepehne, McNee, Raydin et al. Lepehne[8] found the average figure in a series of patients not suffering from jaundice to be 0.15 mg. McNee[10] obtained similar results. Botzian[26] and Wiemer[27] also consider the upper limit of normal 0.75 mg., Mandelbaum,[28] 0.62 mg. (1.25 units) and Haselhorst,[29] 0.5 mg. (1 unit). Strauss and Buerkmann[30] found values between 0.15 and 0.55 mg. in fifty normal patients, with an average of 0.3 mg. Förster and Förstner consider 1 mg. as the upper limit of normal. Greene and his

21. These authors add to 1 part of serum, 1 or 2 parts of colorless acetone; they then centrifugalize it and compare the supernatant liquid with a standard solution of potassium chromate, 1:6,000.

22. Broun, G. O.; Ames, O.; Warren, S., and Peabody, F. W.: J. Clin. Investigation **1**:295, 1924-1925.

23. Meyer, E. C., and Knüpffer, H.: Deutsches Arch. f. klin. Med. **138**:321, 1922 (Förster and Förstner).

24. Van den Berg (footnote 1, reference 1).

25. Van den Bergh (footnote 1, reference 2).

26. Botzian, R.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:549, 1920.

27. Wiemer, P.: Deutsches Arch. f. klin. Med. **151**:154, 1926.

28. Mandelbaum, R.: Monatschr. f. Geburtsh. u. Gynäk. **59**:17, 1922.

29. Haselhorst, G.: München. med. Wchnschr. **68**:174, 1921.

30. Strauss, L., and Buerkmann, W.: Klin. Wchnschr. **1**:1407, 1922.

co-workers [31] at the Mayo Clinic consider 2.0 mg. as the maximum normal. This limit takes care of instances of familial cholemia.

Particular attention was paid to the four individuals (medical students) with the highest values of serum bilirubin—0.8, 1.1, 1.25 and 1.5 mg., respectively—who represent what Gilbert and Lereboullet,[32] in 1906, called simple familial cholemia and what van den Bergh spoke of as physiologic hyperbilirubinemia. In all four there was a yellowish cast to the skin, and the periphery of the sclerae was slightly icteric. In none was the liver or spleen felt. None had ever noticed or had ever been told that he was distinctly jaundiced, except patient 4, who on one occasion, two years ago, had been told that his skin was yellow. There was no instance of unexplained pruritis or definite bradycardia. The specimens of urine were entirely normal, except for the presence of urobilin in traces in two of the individuals and in marked excess in the other two. A questionable increase in erythrocytic fragility was noted

TABLE 2.—*Data of Four Patients Having Highest Serum Bilirubin*

No.	Mg. Bilirubin	Icterus Index*	Red Blood Cells	Per Cent Hemoglobin	Per Cent Reticulated Cells	Urobilinuria	Erythrocytic Fragility†	Retention of Bromsulphalein‡
1	1.5	14	6,400,000	90	0.25	++	0.44-0.36	0
2§	1.25	11	6,000,000	85	0.2	Trace	0.44-0.38	0
3	1.1	12	5,600,000	90	1.0	++	0.42-0.36	0
4	0.8	9	6,000,000	85	0.4	Trace	0.44-0.36 0.42-0.34 (control)	0

* Method of A. R. Bernheim (Icterus Index, J. A. M. A. **82**: 291 (Jan. 26) 1924).
† Technic of Griffin and Sanford (J. Lab. & Clin. Med. **4**: 465, 1918-1919).
‡ Retention in one-half hour. Technic of Rosenthal and White (Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**: 1112 (April 11) 1925).
§ Jewish patient.

in one. A relatively high red cell count was present in three. Van den Bergh [24] has occasionally encountered a palpable spleen in addition to urobilinuria in similar cases and feels that such cases border on chronic hemolytic jaundice. He found the disease more common among the Jewish race and generally encountered values of 1.1 and 1.25 mg.

The observations in the four individuals are tabulated in table 2.

OBSERVATIONS IN DISEASE

1. *Congestive Heart Failure.*—There were twenty-three cases of congestive heart failure—five rheumatic (four mitral lesions and one adherent pericardium); five syphilitic (aortic insufficiency); five hypertensive; six arteriosclerotic; one mitral and tricuspid insufficiency (etiology?) and one of auricular fibrillation associated with a toxic thyroid adenoma (table 3).

31. Greene, C. H.; Snell, W. M., and Walters, W.: Diseases of Liver, Arch. Int. Med. **36**:248 (Aug.) 1925.

32. Gilbert, A., and Lereboullet, P.: Compt. rend. Soc. de biol. **58**:937 and 1007, 1905, quoted by van den Bergh.

The higher values were more frequently encountered in the mitral lesions, an experience similar to that of Fishberg[33] and of Meulengracht,[34] the latter author using the icterus index. In eleven patients, the values were 0.65 mg. or below; of these, nine improved and two died. Of five with a value between 1.0 and 1.35 mg., two were improved and three died. The remaining readings were above 2.0 mg. (five direct increases and two indirect increases); both of the patients having indirect increases and three having direct increases died. The highest value obtained was 4.6 mg. in a case that proved fatal. No bilirubinuria was present in the two patients giving an indirect increase, while bilirubinuria was present in the five giving the direct reaction; there was thus a virtual hemolytic and obstructive type of jaundice present.

TABLE 3.—*Congestive Heart Failure*

No.	Age	Liver (Right Midclavicular Line)	Red Blood Cells	Hemoglobin, per Cent	Jaundice	Died	Mg. Bilirubin		Etiology
							Direct	Indirect	
1	27	10 cm.	5,100,000	70	+	+	2.25	...	Rheumatic
2	20	6 cm.	4,400,000	90	+	+	2.8	...	Rheumatic
3	12	10 cm.	4,200,000	60	+	+	—	2.5	Rheumatic
4	16	4 cm.	4,100,000	70	—	+	—	2.5	Rheumatic
5	32	Edge	5,800,000	90	—	—	—	1.0	Rheumatic
6	48	10 cm.	4,100,000	70	—	—	—	0.5	Syphilitic
7	43	.....	3,800,000	70	—	—	—	0.3	Syphilitic
8	48	10 cm.	5,300,000	70	—	—	—	0.25	Syphilitic
9	49	10 cm.	4,200,000	70	+	+	4.6	...	Syphilitic
10	32	4 cm.	4,000,000	80	+	—	3.0	...	Syphilitic
11	52	6 cm.	3,600,000	80	—	—	—	1.25	Hypertensive
12	64	8 cm.	4,100,000	70	—	+	—	1.0	Hypertensive
13	57	6 cm.	4,800,000	90	—	—	—	0.5	Hypertensive
14	56	—	5,000,000	80	—	+	—	0.65	Hypertensive
15	41	10 cm.	5,400,000	80	—	+	—	1.0	Hypertensive
16	60	—	5,400,000	80	—	—	—	0.5	Arteriosclerotic
17	61	—	3,900,000	70	—	—	—	—0.2	Arteriosclerotic
18	72	—	4,500,000	90	—	—	—	0.25	Arteriosclerotic
19	58	—	5,200,000	80	—	+	—	0.4	Arteriosclerotic
20	62	—	3,900,000	70	—	—	—	—0.2	Arteriosclerotic
21	65	4 cm.	4,700,000	94	+	—	2.5	...	Arteriosclerotic
22	43	10 cm.	5,700,000	80	—	+	—	1.35	Mitral and tricuspid insufficiency
23	68	—	4,200,000	80	—	—	—	0.3	Toxic goiter (auricular fibrillation)

Sections of the livers of the two patients with the hemolytic type of jaundice and of two with the obstructive type were examined by Dr. Richard Austin, but they did not reveal any especial difference in the pathologic picture. All presented a chronic passive congestion with hemorrhage. None of the cases showed demonstrable pulmonary infarcts; their relationship to the jaundice occurring in myocardial insufficiency has been noted by a number of authors (Eppinger,[35] Libman,[36]

33. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80:** 1516 (May 26) 1923.

34. Meulengracht, E.: Deutsches Arch. f. klin. Med. **132:**285, 1920.

35. Eppinger, H., in Kraus and Brugsch: Handb. d. spez. Path. u Therap. **6:**293, 1923.

36. Libman, cited by Fishberg (footnote 33).

Keefer and Resnik [37] and Rich and Resnik [38]). In two instances of jaundice developing after pulmonary infarction, Keefer and Resnik obtained a direct reaction of 2.5 mg.

The mortality in the foregoing cases appears to be directly proportional to the height of the serum bilirubin, an experience similar to that of Bernheim [39] and others, as shown in table 3.

Thus, in virtually one out of five cases with a value of less than 1.0 mg. the outcome was fatal, in contrast to two out of three with a value of 1.0 and more.

In nine of twelve cases showing definite hepatic enlargement, the value of the serum bilirubin was 1 mg. or over. However, the remaining three patients (two with the liver 10 cm. below the costal margin),

TABLE 4.—*Proportion of Mortality to Height of Serum Bilirubin*

Mg. Bilirubin	Number Cases	Mortality
Less than 1.0	11	18.1
1.0 and over	12	66.6

TABLE 5.—*Acute Alcoholism*

No.	Mg. Alcohol per Cc. of Urine*	Coma	Mg. Bilirubin Indirect
1	4.2	+	—0.2
2	3.9	±	—0.2
3	4.3	±	0.2
4	2.0	+	—0.2
5	3.0	+	0.4
6	5.0	+	—0.2
7	4.5	+	0.25
8	5.0	+	—0.2
9	...	+	—0.2
10	3.9	+	—.02
11	5.0	+	—0.2
12	3.0	—	—0.2

* Determinations by Dr. E. Bagen.

who had a value of only 0.6 mg. or less, all recovered, thus illustrating the fact that hepatic enlargement does not necessarily signify retention of bilirubin; similar results have been noted by Fishberg [33] and Andrews.[39a] There was no instance of definite hyperbilirubinemia in the eight cases that did not show enlargement of the liver. Brulé [40] and Fishberg, however, have noted such an increase in the absence of hepatic enlargement in cases of cardiac decompensation. Lepehne [8] and Fishberg [33] have noted that the high values of blood bilirubin occurring in cardiac insufficiency are lowered with an improvement in compensation.

37. Keefer, C. S., and Resnik, W. H.: J. Clin. Investigation **2**:375 and 389, 1926.

38. Rich, A. R., and Resnik, W. H.: Bull. Johns Hopkins Hosp. **38**:75, 1926.

39. Bernheim, A. R.: Icterus Index, J. A. M. A. **82**:291 (Jan. 26) 1924.

39a. Andrewes, C. H.: Quart. J. Med. **18**:19, 1924.

40. Brulé, M.: Recherches sur les ictères, Paris, ed. 3, 1922, p. 117.

2. *Acute Alcoholism.*—In twelve cases of acute alcoholism, an increase in the serum bilirubin was not encountered, but, on the contrary, a tendency toward hypobilirubinemia was noted (table 5). In four of the cases (5, 6, 7 and 8), blood counts and determinations of volume index were made to exclude hydremia and anemia. In cases 5 and 7, the determinations were repeated twelve hours later, with virtually the same results. Whether the patients' levels of serum bilirubin were low before the ingestion of alcohol or whether alcohol stimulates the liver to increased excretion of bilirubin is not known.

3. *Tabes Dorsalis.*—No increase was noted in the serum bilirubin during gastric crisis in three cases of tabes dorsalis (table 6). This

TABLE 6.—*Tabes Dorsalis with Gastric Crisis*

No.	Mg. Bilirubin Indirect	Comment
1	—0.2	During crisis
2	—0.2	During crisis
3	—0.2	During crisis

TABLE 7.—*Lobar Pneumonia with Jaundice*

No.	Age	Lobes Affected	White Blood Cells	Red Blood Cells	Hemoglobin, per Cent	Day of Illness	Day of Jaundice	Mg. Bilirubin Direct
1	23	Right lung	63,000	3,600,000	70	9	?	8.0
2	33	Right middle and lower	12,000	4,600,000	90	9	2	10.7
3	20	Right lung, left lower	17,000	3,000,000	80	8	?	6.3
4	31	Right upper	9,400	2,700,000	65	8	4	4.3
5	34	Right upper	25,000	—	40	7	4	10.0
6	20	Both lower, especially right; left apex, slightly	21,400	4,900,000	90	30 hrs.	?	4.7
7	39	Right lower	10,000	—	—	8	?	10.6
8	33	Right lower	18,600	4,100,000	70	6	?	11.0
9	19	Right lung and left lower	28,300	4,400,000	100	12	3	10.0
10	38	Right lung	16,400	—	—	7	?	3.7
11	31	Right lung	26,000	4,100,000	60	4	?	5.0
12	24	Right upper	29,600	4,500,000	..	8	?	5.0
13	22	Right lower	13,300	4,200,000	90	6	?	14.0
14	40	Left upper; later right upper	21,000	4,400,000	90	10	1	4.0

observation should be of value in differentiating such a crisis from an attack of gallstone colic. According to Meulengracht,[6] there is also not any rise in the serum bilirubin during attacks of renal colic or acute appendicitis.

4. *Acute Lobar Pneumonia (with Jaundice).*—In fourteen cases of jaundice developing in the course of acute lobar pneumonia, the most striking observation was the involvement of one or more lobes of the right lung in thirteen cases, and while the left upper lobe was infiltrated at the time of the onset of jaundice in the fourteenth case, infiltration of the right upper lobe subsequently occurred (two weeks later) (table 7). In the thirteen cases in which the right side was involved, there was associated involvement of the left lower lobe in two cases and slight infiltration of the left apex in the third. Of seven more

patients having pneumonia with jaundice on whom estimations of serum bilirubin were not done, the process was limited to the right side in four; it was present on both sides in two, and in the seventh, while originally present on the left side (lower, then left upper), subsequently involved the right lower lobe twelve days later.

Thus, in 21 cases of acute lobar pneumonia showing jaundice, among a total of 826 patients having lobar pneumonia admitted to the hospital between 1923 and 1926, inclusive, the pneumonic process was present on the right side in all; in two of the cases (initially left-sided), the jaundice preceded recognizable infiltration of the right side. While the constant association of jaundice and pneumonia on the right side occurring in this group of cases may be coincidental, it suggests the possibility of an anatomic basis as a factor in the production of the secondary infectious hepatitis of pneumonia.

Eight of the twenty-one patients died, bearing out Cole's statement [41] that the occurrence of jaundice in acute lobar pneumonia is not of serious prognostic significance.

TABLE 8.—*Chronic Hemolytic Jaundice*

No.	Duration Jaundice	Gall-bladder Disease	Abdominal Pain	Spleen Enlarged	Red Blood Cells	Hemoglobin, per Cent	Fragility Increase	Mg. Bilirubin Indirect
1	8 years	+	+	—	4,800,000	80	—	5.0
2	10 years	+	+	4 cm.	4,300,000	80	—	7.5
3	10 years	±	—	4 cm.	3,900,000	65	—	5.6
4	9 years	—	—	—	2,600,000	50	+	2.8
5	3 years	—	—	Edge	4,600,000	90	+	2.5

The earliest instance of marked hyperbilirubinemia was thirty hours after the onset of the disease (case 6), in which a value of 4.7 mg. was found approximately twenty-four hours prior to the occurrence of bilirubinuria.

5. *Chronic Hemolytic Jaundice.*—All of the cases presented a definite increase in the percentage of the reticulated cells, with marked urobilinuria (slight in case 4), and absence of bile salts and pigment from the urine (table 8).

Only an indirect reaction was obtained, as van den Bergh first pointed out, regardless of the degree of bilirubinemia.

That there is no direct relationship between the fragility of the red cells and bilirubinemia is borne out in cases 2 and 5, several simultaneous determinations being made in the latter (table 9). It is noteworthy that within seventy-two hours after splenectomy the serum bilirubin in this case dropped from a level of 4.2 to 0.35 mg., an experience similar to that reported by Rich and Rienhoff.[42]

41. Cole, R., in Nelson's Loose-Leaf Living Medicine **1**:203, 1924.

42. Rich, A. R., and Rienhoff, W. F., Jr.: Bull. Johns Hopkins Hosp. **36**: 431, 1925.

Evidence of disease of the gallbladder was present in 3, or 60 per cent of the series, a fact in harmony with the observations of W. J. Mayo [43] in a large series of cases. The evidence in cases 1 and 2 consisted of attacks of severe pain in the right upper quadrant and vomiting, with temporary increase in the jaundice plus failure to visualize the gallbladder by Graham's method. Gallstones had been found in case 4 eight years previously, when a cholecystotomy was performed. Patient 3 was operated on for supposed disease of the gallbladder and later for "adhesions," but he did not know what was found or done.

It should be noted that the highest bilirubinemia was encountered with a red cell count of 4.3 million. In the instance of the lowest red cell count (case 4), a value of only 2.8 mg. was found, somewhat contrary to what one would ordinarily expect in this disease. However, the patient also had arterial hypertension with some renal involvement, and thus another factor may have been present in the production of the anemia.

TABLE 9.—*Serum Bilirubin in Case 5*

	Date							
	Feb. 11	March 17	May 11	May 14	May 14	May 17	Sept. 3	March 14
Fragility pt.	0.42-0.32	0.48-0.42	0.44-0.36	...	Sple-	0.48-0.38	0.44-0.36	0.40-0.32
Fragility control....	0.42-0.32	0.42-0.34	0.40-0.32	...	nec-	.....	0.40-0.32	0.40-0.32
Mg. bilirubin.....	2.5	1.0	3.1	4.2	tomy	0.35	1.7	2

The two highest values were obtained in the individuals showing the greatest splenic enlargement. The return of the hyperbilirubinemia in case 5 following splenectomy may be due to the existence of a simple familial cholemia, which van den Bergh hints may in some instances possibly be the forerunner of a hemolytic jaundice. It may be added that the diagnosis in this case was substantiated at the Mayo Clinic. Since splenectomy was performed, the patient has regained his former energy and is able to perform the arduous tasks of a resident surgeon. There has been only a trace of urobilin in the urine on a number of examinations, and the reticulated cell count has remained normal. If nothing were known of the patient's previous history, his case might well be taken for one of simple familial cholemia. It should be added that he has achlorhydria.

6. *Sickle Cell Anemia.*—An indirect increase in the serum bilirubin, similar to that in chronic hemolytic jaundice and pernicious anemia as directly opposed to the results in most secondary anemias, would indicate that the anemia in this disease is hemolytic in character (table 10). In case 2, which showed the highest value in the series, bilirubinuria was not present but marked urobilinuria was found.

43. Mayo, W. J.: Am. J. M. Sc. **171**:313, 1926.

Splenectomy in one case did not effect a disappearance of the hyperbilirubinemia, nor of the "sickling" of the red cells. The latter is perhaps comparable to the persistence of increased erythrocytic fragility following splenectomy in chronic hemolytic jaundice.

The first two of my cases were reported by Alden,[44] while a report of the third is to be published by Mitchell [45] and his associates.

7. *Hereditary Hemorrhagic Telangiectasia.*—In six patients who had hereditary hemorrhagic telangiectasia, a low value of serum bilirubin, similar to that obtained in ordinary secondary anemia, was present (table 11). Apparently, only mechanical loss of blood occurs in this disease.

TABLE 10.—*Sickle Cell Anemia*

No.	Age	Sex*	Color	Red Blood Cells	Hemoglobin, per Cent	Mg. Bilirubin Indirect	Comment
1	4	♂	Black	2,500,000	60	1.0	
2	18	♂	Black	2,000,000	45	4.0	
3	2½	♂	Black	3,000,000	40	1.4 (Oct. 13)	Splenectomy (Oct. 30)
				2,700,000 (Oct. 13)	80	0.65 (Nov. 13)	
				4,000,000	..	1.0 (Dec. 13)	
4	14	♀	Black	1,700,000	30	1.3	

* In this table and table 16, ♂ indicates male; ♀, female.

TABLE 11.—*Hereditary Hemorrhagic Telangiectasia* *

No.	Red Blood Cells	Hemoglobin, per Cent	Mg. Bilirubin Indirect
1	1,800,000	35	0.3
2	4,400,000	..	0.2
3	3,600,000	50	—0.2
4	3,800,000	65	0.3
5	4,200,000	75	0.2
6	4,800,000	70	—0.2

* Mother and five children affected.

8. *Cirrhosis of the Liver.*—The series included sixteen cases, fourteen showing tertiary hepatic syphilis and two showing portal cirrhosis, probably alcoholic (table 12). The clinical diagnoses were based on the criteria set forth by Rolleston [46] and McCrae and Caven,[47] a number of cases being excluded because of insufficient evidence.

Eight of the sixteen patients showed neither jaundice nor increase in the serum bilirubin, while the other eight were jaundiced, five frankly so and three with bile tinged sclerae and mucous membranes, and with a questionable yellow tinge to the skin.

44. Alden, H. S.: Am. J. M. Sc. **173**:168, 1927.

45. Mitchell, A. G.; Bell, A. J., and Kotte, R. H.: Am. J. Dis. Child., to be published.

46. Rolleston, H. D.: Oxford Med. **3**:304, 1921.

47. McCrae, T., and Caven, W. R.: Am. J. M. Sc. **172**:781, 1926.

Six of the eight patients without jaundice had experienced one or more hematemeses in the past and presented a severe degree of secondary anemia. In contrast, only one of the eight jaundiced patients had had a hematemesis prior to the occurrence of the jaundice, and in only two (patient 9 had vomited blood just prior to admission) did a severe secondary anemia exist. In five of the eight cases not showing jaundice,

TABLE 12.—*Cirrhosis Hepatis* *

No.	Age	Hematemesis	Ascites	Liver (Right Midclavicular Line)	Spleen	Blood Wassermann Test	Pathologic Diagnosis	Red Blood Cells	Hemoglobin, per Cent	Jaundice	Mg. Bilirubin	
											Direct	Indirect
1	43	—	—	14 cm.	9 cm.	4 +	—	2,100,000	35	—	—	0.4
2	34	—	0	5 cm.	4 cm.	4 +	—	2,800,000	50	—	—	0.45
3	42	—	—	4 cm.	Edge	—	—	2,400,000	50	—	—	0.5
4	38	—	—	—	4 cm.	4 +	—	2,200,000	30	—	—	0.65
5	42	—	—	—	—	4 +	+	2,500,000	..	—	—	0.3
6	56	—	..	—	—	—	—	2,900,000	50	—	—	—0.2
7	43	0	0	8 cm.	Edge	..	—	4,700,000	90	—	—	—0.2
8	30	—	—	4 cm.	2 cm.	4 +	—	2,300,000	35	+	+	...
9	44	0	—	8 cm.	—	4 +	+	2,900,000	55	+	2.5	...
10	41	0	—	8 cm.	—	—	—	4,000,000	85	+	7.0	...
11	39	0	0	11 cm.	8 cm.	—	—	3,400,000	70	+	6.5	...
12	58	0	—	—	0	—	—	3,900,000	70	+	—	1.75
13	42	0	0	12 cm.	0	—	+	4,800,000	80	+	—	1.5
14	60	—	0	—	—	—	+	3,700,000	45	+	2.5	...
15†	54	0	—	8 cm.	4 cm.	—	—	4,100,000	70	—	—	1.5
16†	55	0	—	—	—	—	+	4,000,000	70	+	—	1.5

* Cases 1 to 14 inclusive showed tertiary syphilis.
† Portal (alcoholic) cirrhosis.

TABLE 13.—*Malignant Disease of the Liver*

No.	Age	Liver (Right Midclavicular Line)	Red Blood Cells	Hemoglobin, per Cent	Primary Site	Mg. Bilirubin		Jaundice	Pathologic Diagnosis
						Direct	Indirect		
1	73	10 cm.	3,900,000	75	Stomach.....	—	0.3	—	+ (N)*
2	65	4 cm.	4,800,000	80	Breast.....	—	0.5	—	— (N)
3	35	11 cm.	4,500,000	90	Pancreas.....	—	0.55	—	+ (N)
4	71	10 cm.	4,300,000	65	Stomach.....	—	0.75	—	—
5	81	4 cm.	4,100,000	90	Stomach.....	—	0.25	—	—
6	48	2 cm.	2,400,000	35	Stomach.....	—	0.25	—	+ (B)†
7	26	4 cm.	2,600,000	35	Stomach.....	—	—0.2	—	+ (B)
8	57	15 cm.	4,500,000	80	Gallbladder.....	—	—0.2	—	+ (N)
9	47	6 cm.	3,600,000	80	?.....	—	1.0	—	+ (N)
			1,300,000	30	(Carcinoma).....	—	—0.2	—	
10	4½ mo.	.....	1,700,000	55	Liver (hepatoma)..	—	0.6	—	+ (N)
11	67	10 cm.	4,000,000	85	Stomach.....	+	...	+	+ (N)
12	45	11 cm.	4,300,000	50	Pancreas.....	+	...	+	+ (N)
13	56	10 cm.	.....	80	Undetermined.....	3.1	...	+	+ (B)
14	70	15 cm.	4,000,000	70	Bile duct.....	19.5	...	+	+ (N)
15	69	4 cm.	3,200,000	70	Gallbladder.....	15.0	...	+	+ (B)
16	68	2 cm.	.....	75	Stomach.....	20.0	...	+	+ (B)
17	66	Nodular	3,900,000	60	Iris.....	4.6	—	+	+ (N)

* (N) indicates necropsy.
† (B) indicates biopsy.

a hyperbilirubinemia was absent, in spite of considerable enlargement of the liver. In three of these, a severe anemia existed. While it is realized "that more than three-fourths of the liver can be abruptly obstructed without causing even a ripple on the clinical surface of things" (Rous [48] and McMaster and Rous [49]), a relationship of the

48. Rous, Peyton: Am. J. M. Sc. **170**:625, 1925.
49. McMaster, P. D., and Rous, Peyton: J. Exper. Med. **33**:731, 1921.

level of the serum bilirubin as well as the occurrence of jaundice in cases of hepatic cirrhosis to the amount of circulating hemoglobin and blood cells appears to be suggested, as in the cases of hepatic malignant disease studied.

9. *Malignant Disease of the Liver.*—There were seventeen cases, seven with jaundice and ten without (table 13). Among those without jaundice, there were only two relatively high values, viz., 0.75 and 1 mg., the remainder being 0.6 mg. or less. In eleven cases of carcinoma of the liver without jaundice (diagnosis pathologically confirmed) Greene and his associates [9] found two presenting bilirubin values above 2 mg. and three showing values between 0.9 and 1.6 mg.; they feel that while the determination of serum bilirubin may not show any increase in some cases, it is nevertheless of definite value in the early diagnosis of carcinoma of the liver.

TABLE 14.—*Acute Catarrhal Jaundice*

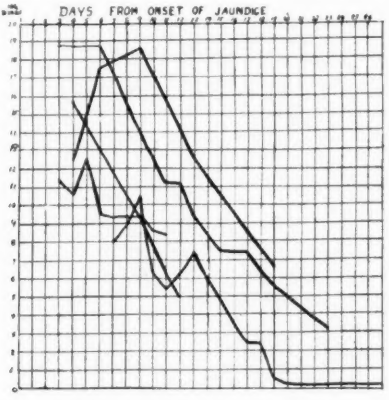
Number	Age	Liver (Right Midclavicular Line)	Spleen	Day of Jaundice	Mg. Bilirubin Direct
1	9	6 cm.	0	9	6.5
2	25	0	0	10	10.0
3	6	0	0	4	7.0
4	40	9 cm.	Edge on inspiration	21	4.0
5	37	1½ cm.	0	6	15.6
				14	18.7
6	26	0	0	Day preceding	4.0
7	36	0	0	7	10.0
8	33	4 cm.	0	24	2.7
9	15	2 cm.	Edge	4	12.0
10	42	8 cm.	0	25	3.0
11	19	2 cm.	0	4	15.6
12	33	0	0	4	8.0
13	44	4 cm.	Edge	2	18.7
14	17	6 cm.	6 cm.	7	9.4
15	44	5 cm.	Edge	4	12.5

The absence of hyperbilirubinemia in the presence of hepatic malignant disease has also been noted by Lepehne,[8] Meulengracht,[34] and Andrewes.[39a] In the four cases showing the lowest readings in bilirubin, a severe secondary anemia was present. In four of Greene's eleven cases in which the values were 0.2 mg. or less, a severe secondary anemia existed in three. On the other hand, it is of interest to note that a severe secondary anemia was not present in five of the seven cases showing jaundice in which counts were recorded, and in all fourteen of such cases reported by Greene.

It is of great interest to note a fall in serum bilirubin in one of the cases (carcinoma), accompanying a drop in the hemoglobin and in the number of red cells. Greene [18] has also seen the serum bilirubin fall in malignant disease of the liver.

10. *Acute Catarrhal Jaundice.*—Fifteen cases of acute catarrhal jaundice were studied, serial estimations being made from day to day in five (table 14). The mean value during the first week of jaundice was

approximately 13 mg.—a deep jaundice; during the second week, an average of approximately 9 mg., a moderately deep jaundice, and during the third week, an average of approximately 4 mg., representing a relatively mild jaundice. In the light of these estimations, the mechanism of acute catarrhal jaundice appears frequently to be one of sudden marked disablement of the liver in regard to the excretion of bilirubin, lasting frequently for less than a week, with subsequent rapid resumption of function. This is in accord with the "two distinct phases" of the disease described by Jones and Minot [50] in an extensive study of twenty-six cases, who also found the concentration of serum bilirubin during the disease to be a reciprocal of the concentration of bile pigment in the duodenum.



Acute catarrhal jaundice.

During the first week of jaundice, hepatic enlargement was detected in seven cases, an associated splenic enlargement being present in four instances. The average value of bilirubin in the three cases showing only hepatic enlargement was 13.06 mg., virtually the same as the average value in the four cases showing both splenic and hepatic enlargement (13.15 mg. per cent). In sharp contrast to this is the average of 7.25 mg. per cent in the four cases showing neither apparent hepatic nor splenic enlargement, in which determinations were also made during the first week of jaundice. This suggests that the swollen condition of the liver may indicate a greater degree of functional impairment in regard to the excretion of bilirubin.

While all the reactions in this series of cases were of the direct type, Schiff and Eliasberg,[51] in studying a group of thirty cases occurring in

51. Schiff, E., and Eliasberg, H.: Klin. Wchnschr. **38**:1891, 1922.
50. Jones, C. M., and Minot, G. R.: Boston M. & S. J. **189**:531, 1923.

children during the winter of 1921 and 1922, found that between October, 1921, and January, 1922, all the serums gave the delayed direct reaction only, whereas a prompt direct reaction was obtained in all subsequent cases, without the least apparent change in the clinical picture.

11. *Stone Obstructing the Common Duct.*—Four cases of stone obstructing the common duct were studied (table 15). In three, there was a marked "direct" increase in the serum bilirubin, while in the fourth, one of Charcot's intermittent hepatic fever, a transient slight increase during the attacks of pain and chills occurred. In this patient, the relation of bilirubinemia to temperature, chills, pain and number of leukocytes is noteworthy and is given in table 16.

TABLE 15.—*Stone Obstructing Common Duct*

No.	Age	Sex	Pathologic Diagnosis	Clinical Jaundice	Red Blood Cells	Hemoglobin, per Cent	Mg. Bilirubin Direct
1	72	♂	+	+	4,700,000	80	15.0
2	45	♀	+	5 weeks	4,400,000	75	9.4
3	36	♀	—	7 weeks	.....	85	26.0
4	43	♀	+	—	.....	75	1.8

TABLE 16.—*Charcot's Intermittent Hepatic Fever (Case 4)*

Time	Temperature	Leukocytes	Pain	Chill	Mg. Bilirubin	
					Direct	Indirect
1/3/27 4:00 p.m.	98.4	9,400	0	0	—	0.6
1/5/27 7:00 p.m.	103.2	17,800	+	+	1.8	...
1/6/27 5:30 p.m.	99.4	9,000	0	0	—	0.4

Walters [52] has noted the frequency of stone in the common duct without jaundice. More remarkable is the fact that a stone may be present without even a distinct increase in the serum bilirubin, as in case 4 of this series (between attacks) and in one of eighteen cases of chronic cholecystitis studied.

12. *Tumor Obstructing the Common Bile Duct.*—Of particular interest in this series are three instances of a fall in serum bilirubin when a tumor obstructed the common bile duct (table 17). In two, a pathologic diagnosis of carcinoma of the pancreas was made, while in the third a firm tumor of the papilla of Vater, measuring 2 by 5 cm., and thought to be malignant, was encountered at operation. Word was received later from this patient's physician that the jaundice had completely disappeared.

It is of interest to note in case 4 a decline in the hemoglobin and red cell count accompanying the drop in the serum bilirubin, suggesting

52. Walters, Waltman: Surg. Gynec. Obst. **42**:453, 1926.

a possible cause for the latter. This is in accord with the experiments of Rous and Drury [53] in ligation of the common duct, which Poer and I [54] have had occasion to verify in a number of animals. The appearance of the skin on May 7 was one of mixed green and black jaundice, replacing the yellow tint noted February 4, and yet the bilirubinemia was at its lowest level. This, of course, is only another argument for the importance of the estimation of serum bilirubin. McNee [10] mentions a similar experience.

In case 5, it was surprising to note a serum bilirubin value of only 4 mg. (determinations on three successive days), with a jaundice of a month's duration. The tumor may have been of an inflammatory nature. It is unfortunate that autopsy was not obtained in this case.

TABLE 17.—*Tumor Obstructing Common Duct*

No.	Age	Diagnosis	Duration of Jaundice	Died	Red Blood Cells	Hemoglobin, per Cent	Mg. Bilirubin Direct
1*	72	Operative	?	+	4,800,000	65	9.3 (Sept. 3)
							13.8 (Sept. 9)
2*	66	Pathologic	5 weeks	+	.....	60	20.0
3*	67	Pathologic	2 weeks	—	5,100,000	74	15.0 (Feb. 4)
					.....	..	17.7 (Feb. 14)
					3,400,000	50	5.0 (May 9)
4*	51	Operative	4 weeks	+	4,900,000	70	4.0 (Aug. 31)
							4.0 (Sept. 2)
5*	88	Clinical	?	+	5,000,000	70	9.4
6†	59	Operative	?	—	.....	..	7.5 (Oct. 5)
							12.5 (Oct. 16)
							9.1 (Oct. 30)
							6.3 (Nov. 10)

* Tumor of head of pancreas.
† Exploratory laparotomy showed a firm mass, 2 by 5 cm., at papilla of Vater, with dilatation of common duct. The jaundice eventually disappeared.

SUMMARY

The original observation of Hijmans van den Bergh that increase of serum bilirubin during obstructive jaundice gives a "direct" reaction with Ehrlich's diazo reagent and that increase in hemolytic types of jaundice gives only an indirect reaction has been confirmed.

One milligram per hundred cubic centimeters of serum may be safely considered the upper limit of normal with values between 0.6 and 1 mg. as possibly indicative of increase. The values are somewhat higher among males than females. Values above 1 mg. are encountered in new-born infants.

Estimations of serum bilirubin are of prognostic value in congestive heart failure, levels exceeding 1 mg. per cent being frequently followed by fatal termination. Hepatic enlargement does not necessarily signify hyperbilirubinemia.

53. Rous, Peyton, and Drury, D. R.: J. Exper. Med. **41**:601, 1925.
54. Poer, H. D., and Schiff, Leon: Unpublished data

Low values of serum bilirubin were noted in acute alcoholism. Whether this is due to stimulation of excretion of bilirubin is not known.

No increase in the serum bilirubin occurs during the gastric crises of tabes dorsalis, in contrast to attacks of acute gallstone colic.

The constant association of right-sided lesions in lobar pneumonia with the incidence of jaundice in 21 of 826 cases suggests an anatomic factor as possibly operative in the production of hepatitis with jaundice in this disease.

In chronic (splenomegalic) hemolytic jaundice, there may not be any definite relationship between the degree of bilirubinemia and the erythrocytic fragility at a given time. There is evidence substantiating the observation of van den Bergh that certain instances of physiologic hyperbilirubinemia may show some of the characteristics of hemolytic jaundice.

In sickle cell anemia as in chronic hemolytic jaundice (and also pernicious anemia), the serum bilirubin shows an increase of the "indirect" type of van den Bergh.

In hereditary hemorrhagic telangiectasia, relatively low values in serum bilirubin are obtained, as in ordinary secondary anemias.

In acute catarrhal jaundice, there is a tendency for the highest serum bilirubin levels to occur in cases showing demonstrable hepatic enlargement, suggesting in the latter instance a greater degree of functional impairment of the liver.

There is evidence suggesting that the level of the serum bilirubin and the occurrence of jaundice in cases of hepatic malignant disease and cirrhosis may depend on the amount of hemoglobin and the number of red cells circulating in the blood.

The level of serum bilirubin may drop and the jaundice may diminish in the presence of obstruction of the common bile duct by tumor and also in carcinoma of the liver. A simultaneous drop in the hemoglobin and number of red blood cells has been noted in some cases.

DIETARY FACTORS THAT INFLUENCE THE DEXTROSE TOLERANCE TEST

A PRELIMINARY STUDY *

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The dextrose tolerance test is now being extensively employed as a diagnostic procedure. It is most beneficially used in the differentiation of mild diabetes mellitus and renal diabetes. It is also being used, and is believed to be of diagnostic value, in many pathologic conditions, such as encephalitis, malignant tumor, pituitary and thyroid dysfunctions and nephritis.[1]

Although it is definitely established as a diagnostic procedure, there is some diversity of opinion concerning what constitutes a normal response to the oral administration of dextrose. Some writers state that in a healthy person there may be a postprandial rise in blood sugar of from 14 to 16 per cent and a return to the normal within two hours.[2] There are other writers [3] who consider a postprandial hyperglycemia of 20 per cent within normal limits. It is generally believed that the persistence of the postprandial hyperglycemia is of more diagnostic significance than the degree of hyperglycemia.[4] In early cases of diabetes the blood sugar curve rises higher, stays up for a longer time and does not return to normal for several hours. Macleod says that "slight deviations from the normal must not be given too much weight in diagnosis, since they may occur in other diseases or even in perfectly normal persons." [5]

All who have studied dextrose tolerance curves have noted the variability exhibited by normal persons, to say nothing of those who are

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* From the Departments of Internal Medicine and Physiology, Baylor University, College of Medicine.

1. Gray, Horace: Blood Sugar Standards in Conditions Neither Normal nor Diabetic, Arch. Int. Med. **31**:259 (Feb.) 1923. John, H. J.: Ann. Clin. Med. **5**:340, 1926. Friedenwald, J., and Grove, J. G.: Am. J. M. Sc. **33**:163, 1922. Paullin, J. E., and Sauls, H. C.: South. M. J. **15**:249, 1922. Mosenthal, Herman O.: M. Clin. N. Amer. **9**:549, 1925.

2. Mosenthal (footnote 1, fifth reference). Macleod: Physiology and Biochemistry in Modern Medicine, ed. 5, St. Louis, C. V. Mosby Company, 1926, p. 876.

3. Hale-White, R., and Payne, W. W.: Quart. J. Med. **19**:393, 1926. Gilbert, Max; Schneider, Hans, and Bock, Joseph C.: J. Biol. Chem. **68**:629, 1926.

4. Mosenthal (footnote 1, fifth reference). John, H. J.: J. M. Research **4**:255, 1923.

5. Macleod (footnote 2, second reference).

diseased. These variations have been discussed and explained in different ways.[6]

It occurred to me that perhaps the character of the food and the amount of water that a person had been consuming for a few days prior to the time the tolerance test was made might be factors that would influence the dextrose tolerance curve. If these factors should prove to be capable of altering a tolerance curve, they could be controlled. This would eliminate some of the confusing variability that is so frequently observed. It was these thoughts that lead to the following experiments.

Young, healthy, male medical students were used to study the effect of different preceding diets. Four groups were formed. The subjects in one group were given a protein diet, those in another a fat diet, those in a third a rich carbohydrate diet, and those in the fourth group were not given any food—the starvation group. Those on the protein diet received only lean meat and the whites of eggs. The students on the fat diet received only olive oil, butter, mayonnaise made with egg yolk, and 20 per cent cream. Those in the group fed on carbohydrates were allowed sugar, candy, pastry, white bread, baked potatoes, syrup, bananas, rice and oatmeal. These diets were followed for two days. Meals were taken at the usual hours, and eating between meals was allowed, provided the diets were followed. Those in the starvation group did without food for two days. On the morning of the third day, each student was given by mouth 1.75 Gm. of dextrose per kilogram of body weight, on an empty stomach. Determinations of blood sugar were made from samples of venous blood removed immediately before the dextrose was given, and at 30, 60 and 120 minute intervals following its administration. I made all determinations of blood sugar by the Folin-Wu method.[7]

The results of these tests are listed in tables 1, 2, 3 and 4, and in charts 1, 2, 3 and 4. It will be noted that the curves are strikingly different. The persons who starved and those who were placed on the fat diet present the most abnormal responses to the administration of dextrose. In no instance did the blood sugar return to normal within two hours. The most atypical curve of these two groups is that of subject W, whose blood sugar rose to 0.286 mg. per hundred cubic centimeters of blood at the two hour observation. This student was nauseated, which probably explains not only the delayed rise, but also

6. Mosenthal (footnote 1, fifth reference). McCaskey, G. W.: The Basal Metabolism and Hyperglycemic Tests of Hyperthyroidism, J. A. M. A. **73**:243 (July 26) 1919. Rohdenburg, G. L.; Bernhard, A., and Krebbiel, O.: Am. J. M. S. **159**:577, 1920.

7. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

TABLE 1.—*Results of Dextrose Tolerance Tests on Four Normal Young Adults (Medical Students) Who Had Been Eating Only Proteins for Two Days Prior to Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
S	23	95	69	143	148	154
T	25	140	75	148	182	...
C	25	110	62	125	168	155
Mc	25	136	71	155	172	125

TABLE 2.—*Results of Dextrose Tolerance Tests on Five Normal Young Adults Who Had Been Placed on the Fat Diet for Two Days Prior to the Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
W	26	71	69	100	95	286
B	25	137	78	143	178	133
S	23	119	80	170	232	190
B2	21	105	95	222	219	170
J	22	119	80	143	195	200

TABLE 3.—*Results of Dextrose Tolerance Tests on Eight Normal Young Adults Who Had Been Placed on the Carbohydrate Diet for Two Days Prior to Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
C	23	85	74	111	125	111
N	25	115	78	111	101	88
J	24	126	75	85	97	85
A	22	141	80	148	111	85
F	25	125	80	121	143	105
Jack	24	165	98	148	108	100
J2	22	119	82	121	114	82
S	23	119	89	111	73	83

TABLE 4.—*Results of Dextrose Tolerance Tests of Five Normal Young Adults Who Starved for Forty-Eight Hours, Only Water Being Taken*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
J	24	124	71	133	167	235
A	22	145	61	143	182	229
M	25	143	58	114	100	129
D	25	149	67	113	178	131
R	21	139	72	157	242	174
C	23	119	74	211	200	205

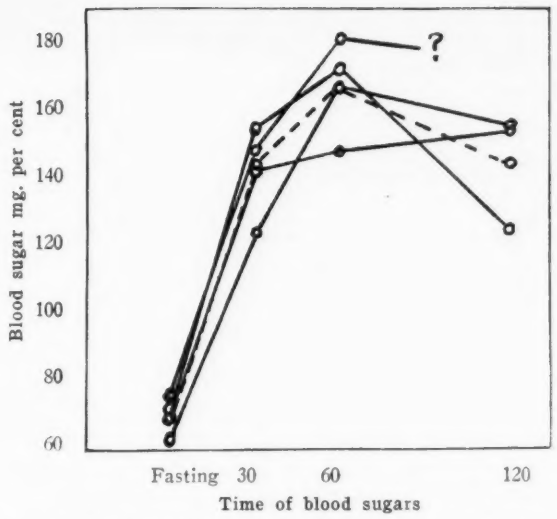

Chart 1.—Graph showing dextrose tolerance curves of four normal young adults who had been eating a protein diet for two days. The dash line in all charts is the average or type curve.

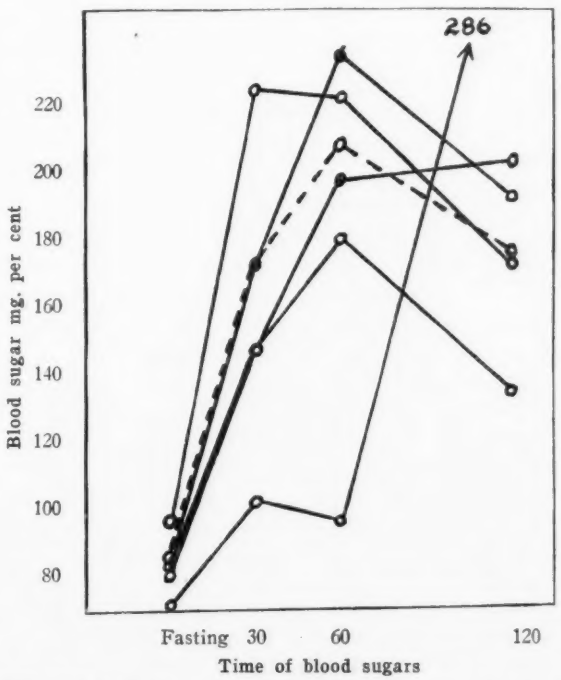

Chart 2.—Graph showing dextrose tolerance curves of five normal young adults who had been eating a fat diet for two days.

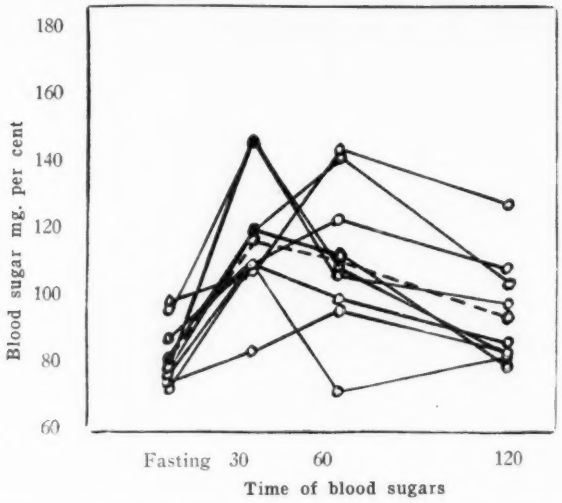

Chart 3.—Graph showing dextrose tolerance curves of nine normal young adults who had been eating a rich carbohydrate diet for two days.

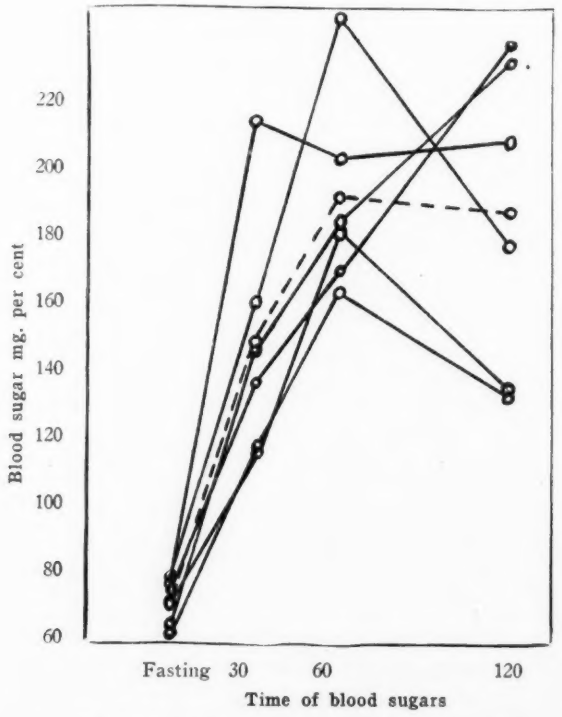

Chart 4.—Graph showing dextrose tolerance curves of six normal young adults who did without food for two days, taking only water.

the slight drop at the one hour observation. This effect of nausea has been pointed out previously.[8]

The groups fed on protein and on carbohydrates, especially the latter, showed a marked contrast to the other groups. Judged by some standards, none of the curves for the protein group should be considered normal. Those in the carbohydrate group are all strikingly within normal limits; in fact, the highest postprandial rise in this group was to a level of 0.148 mg. per hundred cubic centimeters of blood. The highest two hour observation was to 0.111mg.

A better comparison of these groups is obtained by examining table 5 and chart 5 in which are contained the average or type curves of each group. It will be noted that those students who were on the carbohydrate diet exhibited a marked increase in sugar tolerance and those on a protein diet a slight decrease in tolerance, while those who were placed on the fat diet and those who were starved manifested a definite

TABLE 5.—*Table Showing Average Dextrose Tolerance Curves or Type Curves of the Students in the Four Different Dietary Groups*

	Blood Sugar Mg. per 100 Cc.			
		After Dextrose		
Diet Groups	Fasting	30 Minutes	60 Minutes	120 Minutes
Fats*	83	170	206	173
Protein	69	143	167	145
Carbohydrate	84	118	113	96
Starvation	67	145	188	184

* Averages excluding curve of subject W, who was nauseated.

decrease in sugar tolerance. The differences in the average fasting blood sugars are noteworthy. The blood sugar in those of the protein and starvation groups was distinctly lower than that of the members of the fat and carbohydrate groups.

Because of the great difference in these groups, those students on the fat diet and those in the starvation group who showed the most extreme responses were placed on the carbohydrate diet. Similiarly, those in the carbohydrate group who showed an extreme response were placed on starvation restriction. This was obviously done to determine whether the curve of a person could be changed significantly by diet. The results are presented in table 6 and in charts 6 and 7.

Comparison of the curves of these five students is striking. The curves of all who had been placed on carbohydrate diets manifested a definite increase in their sugar tolerance. When three of these (the three most extreme) were placed on starvation restrictions, the curves were notably abnormal; there was a marked postprandial hyperglycemia.

8. Hale-White and Payne (footnote 3, first reference).

which persisted at the end of two hours; in other words, what was an increased sugar tolerance following the carbohydrate diet became a definitely decreased tolerance following two days of starvation. The remaining two persons who were placed on the fat diet showed a similar decreased tolerance. It should be stated that an interval of at least one week was allowed between the tolerance tests performed on the same subject.

It is plain from the foregoing experiments that the dextrose tolerance test may be significantly affected by the character of food taken prior to

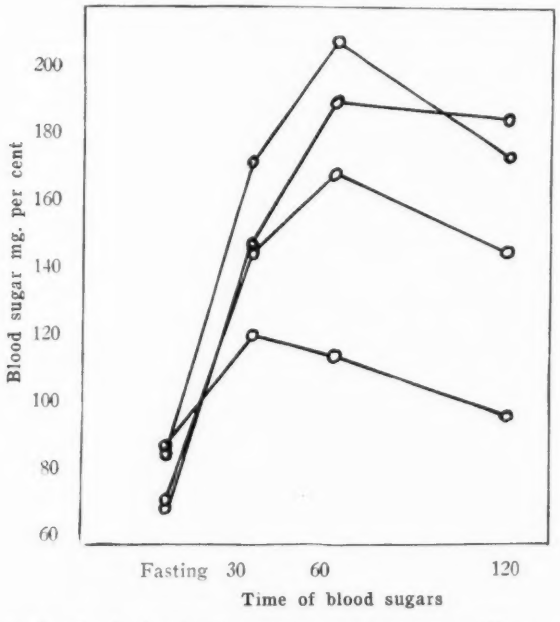

Chart 5.—Graph showing the average or type curves (figures in table 5). Reading from below upward on the two hour ordinate, the curves are as follows: first, carbohydrate; second, protein; third, fat, and fourth, starvation.

the test. Practically, this means that a standardized diet should be worked out to be followed prior to the performance of the dextrose tolerance test. It is reasonable to believe that if a dextrose tolerance curve can be so materially altered by two days of such restriction of the diet as has been shown, that a standardized diet would have the tendency to cause a less variable response. In this connection it is possible that some of the atypical curves that have been noted in different pathologic conditions may in reality be due to the diets indicated and

taken in such states. Likewise, some of the slightly abnormal curves noted in healthy persons may have the same basis of explanation.

Dogs were used for the purpose of studying the effect of hydration and dehydration on dextrose tolerance. To dehydrate the animal, all water was withheld for two days. To increase the body fluids, 500 cc. of physiologic sodium chloride was injected intraperitoneally on the day preceding the test, and 350 cc. more was injected two hours before

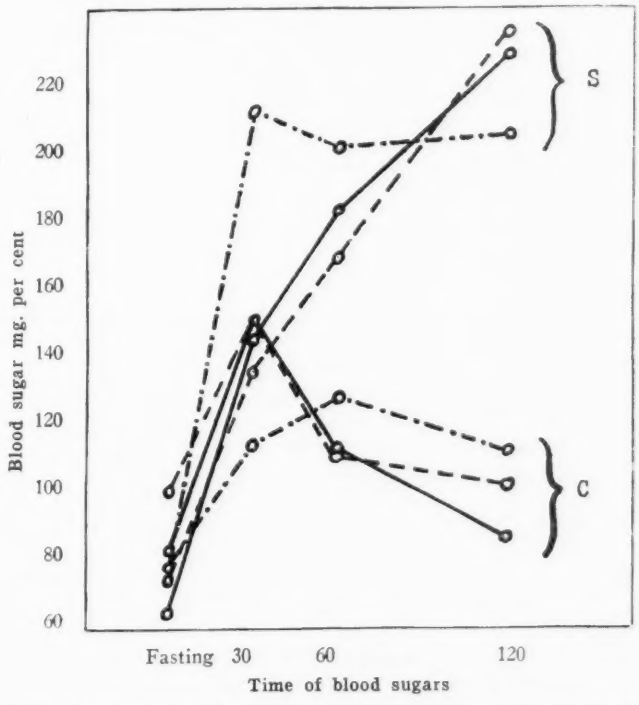

Chart 6.—Graph showing two curves for each of three normal young adults. In one instance—the curves marked S—the students were starved for two days prior to the test; in the other instance—the curves marked *C*—they were fed the carbohydrate diet. Similar lines represent the same subjects.

the dextrose was administered.[9] All dogs were given 2 Gm. of dextrose per kilogram of body weight by stomach tube. The dextrose was diluted with water to make a 20 per cent solution. Samples of blood were drawn as already described for medical students. All determinations were made by Mr. R. W. Lackey of the physiology department. The

9. Andrews, Edmund: Water Metabolism; Sugar Metabolism in Dehydration, Arch. Int. Med. **38**:136 (July) 1926.

Hartmann-Shaffer method was used.[10] All dogs received a mixed diet containing varying proportions of meat, bread and vegetables.

In tables 7 and 8 are listed the results obtained on five hydrated and two dehydrated dogs, respectively. The same results are presented graphically in charts 8 and 9. The dash line in each chart is the average

TABLE 6.—*Table Showing the Dextrose Tolerance Figures of Five Medical Students, Each of Whom Was Placed on Two Different Diet Restrictions, as Indicated, for Two Days Prior to the Tests. An Interval of at Least One Week Was Allowed Between Tests on the Same Individual*

				Blood Sugar Mg. per 100 Cc.			
					After Dextrose		
Subject	Age	Diet	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
A	22	Starvation	145	61	143	182	229
		Carbohydrate ..	141	80	148	111	85
Jack*	24	Starvation	124	71	132	167	235
		Carbohydrate ..	165	98	148	108	100
C*	25	Starvation	119	74	211	200	205
		Carbohydrate ..	85	74	111	125	111
J	22	Fat	119	80	143	195	200
		Carbohydrate ..	119	82	121	114	82
S	23	Fat	119	80	170	232	190
		Carbohydrate ..	119	80	111	73	83

* It will be seen that the amounts of dextrose given to students Jack and C differed for the two tests. This was due to an error in the arithmetic. It is noteworthy that these errors varied in such a way as to make the effect inconsequential.

TABLE 7.—*Results of Dextrose Tolerance Test on Five Dogs That Had Received 850 cc. Physiologic Sodium Chloride Intraperitoneally Prior to the Test*

		Blood Sugar Mg. per 100 Cc.			
			After Dextrose		
Subject	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
Dog 1.....	20	115	112	171	166
Dog 2.....	20	100	118	126	113
Dog 3.....	20	113	125	132	156
Dog 4.....	28	93	107	134	133
Dog 5.....	30	100	150	149	140

TABLE 8.—*Results of Dextrose Tolerance Test on Two Dogs That Had Not Received Any Water for Two Days Prior to the Test*

		Blood Sugar Mg. per 100 Cc.			
			After Dextrose		
Subject	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
Dog 1.....	25	87	169	201	113
Dog 2.....	32	90	139	162	148

curve. Three interesting differences are noted in the comparison of these two groups: First, there seems to be a lower blood sugar in the dehydrated animals while fasting; second, the postprandial hyperglycemia is distinctly less at the thirty minute observation in the hydrated

10. Hartmann, A. F., and Schaffer, P. A.: J. Biol. Chem. **45**:368, 1920.

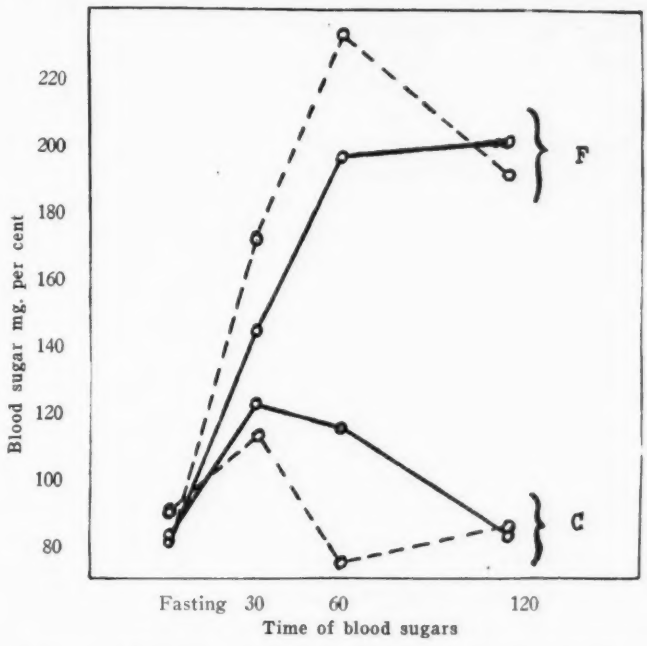

Chart 7.—Graph showing two curves each of two normal young adults. In one instance—the curves marked *F*—the students were fed the fat diet for two days prior to the test; in the other instance—the curves marked *C*—they were fed the carbohydrate diet. Similar lines represent the same subjects.

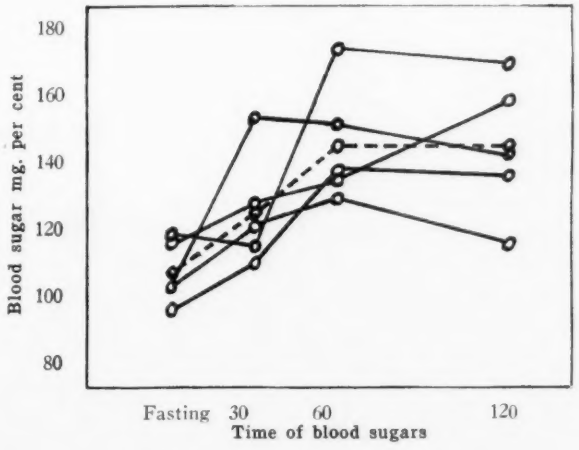

Chart 8.—Graph showing sugar tolerance curves of five hydrated dogs. These animals received 850 cc. of physiologic sodium chloride intraperitoneally.

dogs; and third, there seems to be a tendency toward a delayed return to normal at the two hour period in the hydrated animals. It will be noted that one hydrated dog (dog 5, table 7) showed a marked thirty minute rise in blood sugar as compared to the others in this group. This animal was extremely nervous. Every time he was handled he would become rigid and remain so until placed back in his cage. The factors involved in this phenomenon may explain the comparatively abrupt thirty minute rise in blood sugar.

It is unwise to conclude much from so few observations. It is believed, however, that the really significant result of this experiment is

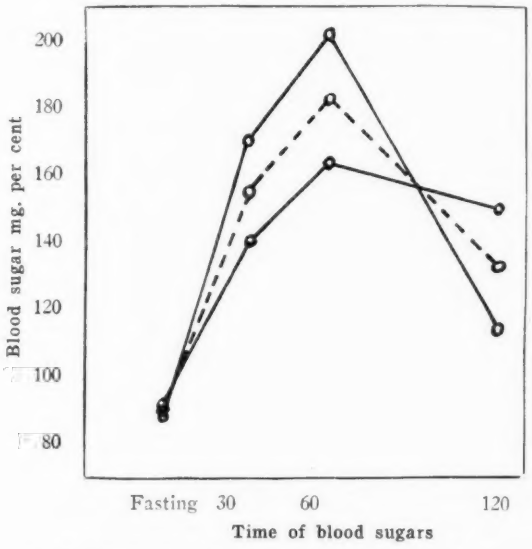

Chart 9.—Graph showing dextrose tolerance curves of two dehydrated dogs. All fluids were withheld for two days.

the delayed initial rise of blood sugar in the hydrated animals. This result is most probably explained on the basis that a mild transient hydremia was produced by intraperitoneal injections of physiologic sodium chloride. More experiments are being performed on hydrated and on dehydrated animals in which the diets are standardized.

COMMENT

It may be stated with reasonable accuracy that the major portion of the dextrose ingested during a dextrose tolerance test is converted into glycogen. The height of the postprandial hyperglycemia, the rapidity of the rise and the persistency of the hyperglycemia may be said to be

dependent on the degree of activity of this glycogenic function. Recent experimental evidence has been accumulated which tends to ascribe a strictly anabolic function to insulin.[5] Lawrence [11] has recently presented good experimental evidence favoring the anabolic function of insulin. By this conception, that is, that insulin has principally a glycogenic function, one may readily explain the behavior of the dextrose tolerance curves obtained not only in the subjects in this study, but also in healthy persons and in patients with diabetes mellitus. One assumption, however, is necessary; namely, that the ingestion of carbohydrates activates an intermediate hormone which in turn stimulates the production of insulin. This is certainly reasonable from a physiologic point of view.

With these points in mind it may be said, in explanation of the normal dextrose tolerance curve, that when dextrose is taken, a hormone is produced which stimulates the production of insulin. The result is only a moderate postprandial rise in blood sugar until the insulin that has been produced has caused active glycogenesis.[12]

In health and as a result of daily eating of the usual mixed diet, this mechanism is working smoothly and flexibly; in other words, the response to carbohydrate ingestion is normal. In case of diabetes, although the hormonic response is normal after the ingestion of dextrose, the amount of insulin that is produced is insufficient to store the dextrose as glycogen, and there is a resultant hyperglycemia and a prolonged curve.

In the curves of the subjects fed on carbohydrate there is an insignificant rise in the blood sugar. This phenomenon, therefore, may be explained by the more active functioning of the hormone stimulating process as a result of an excessive intake of carbohydrates. Consequently, when dextrose was administered, there was no delay in this mechanism, and the stimulation with insulin was more prompt; the result was quick and active glycogenesis.

In those persons who were on protein diets only a slight variation from the normal was found in their response to dextrose. This may possibly be explained on the basis of the carbohydrate content of protein.

In the next group of patients, namely, those receiving fats, the curves fall just where one would expect them to according to the theory proposed. As a result of much ingestion of fat, the activation of the insulin stimulating hormone has been reduced. This would cause a sluggish response when dextrose is ingested; therefore, a rather steep rise in the blood sugar occurs until the insulin stimulating process has been completed.

11. Lawrence, R. D.: Quart. J. Med. **20**:69 (Oct.) 1926.

12. This term is used rather loosely. I am aware of other probable actions of insulin (reference 5).

What has been said of the curves for the subjects on the fat diet may be said for those of the subjects in the starvation group. It is interesting to note that the average curve for the subjects fed on fats showed evidence of a slightly quicker response, that is, a reduction in blood sugar, than did the average curve for the starvation group. This may possibly be due to the small percentage of carbohydrate that fat yields.

Joslin, as well as others, for a long time has stressed the overeating of starches and sugars as important etiologically in diabetes mellitus. The foregoing results tend to strengthen this belief. Whatever lies behind the innate desire for sweets, overeating of them by some persons may impair an inherently weakened insulin producing organ. As a result, when glycogenesis is lessened, the storage of fat increases and the weight increases, an almost invariable fact in the anamnesis of any diabetic person. Diabetes mellitus follows varying periods of obesity.

CONCLUSIONS

1. The dextrose tolerance test, as usually employed, has been shown to be materially influenced by different antecedent foods or diets, and to some degree by the preliminary intake of water. It is suggested that a standardized antecedent diet might eliminate the variability produced by different foods. It is further suggested that some of the dextrose tolerance curves believed to be peculiar to different pathologic conditions might result from the diets indicated or taken in such conditions.

2. The principal effect of hydration or dehydration on the dextrose tolerance curve appears to be a delayed thirty minute postprandial rise in blood sugar in hydrated animals. This was interpreted on the basis of a transient hydremia.

3. Dextrose tolerance tests performed on medical students are shown to vary definitely with the character of the antecedent diet. Four different types of curves are presented: the protein, fat, carbohydrate and starvation curves. These curves are distinctly different and are obtained by simply restricting the diet to protein, fat, carbohydrate and starvation for two days prior to the test.

CHEMICAL STUDIES IN TUBERCULOSIS

I. PLASMA PROTEINS, CHOLESTEROL AND CORPUSCLE VOLUME *

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Medical literature reveals extensive work on cholesterol and plasma protein content of the blood in health and in various diseases, but only a limited number of the reports contain data on pulmonary tuberculosis. Since the onset and the course of development of tuberculosis are comparatively slow, the changes in the blood are likewise slow, in striking contrast to the rapid changes found in pneumonia. As a result of this gradual change, various stages of tuberculosis present chemical pictures as opposite as those found in different diseases. Therefore, to formulate definite conclusions regarding chemical changes in the blood, repeated examinations supplemented with clinical observation should be made on subjects representing all stages of tuberculosis.

The purpose of this work is to ascertain a possible relationship of the plasma proteins, cholesterol and corpuscle volume to the different stages of tuberculosis. Single determinations were made on seventy-one patients, and repeated determinations on thirty-eight.

METHODS

The blood was drawn before breakfast from the antecubital vein in a Keidel tube containing 2 mg. of neutral potassium oxalate per cubic centimeter of blood. The cholesterol was determined in the whole blood, and the proteins were determined in the plasma. For analyses the standard methods for plasma proteins,[1] cholesterol[2] and cell volume[3] were employed. Analyses were made in duplicate, and satisfactory checks were obtained in all results reported. The results are given in table 1.

COMMENT

The corpuscle volume depends on two factors: the number and the size of the erythrocytes. A low erythrocyte value in tuberculosis is always accompanied by a low corpuscle volume, but a low corpuscle volume is not always accompanied by a low erythrocyte count. In fact,

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* From the Research Laboratories, Chemical Department, of the City of Chicago Municipal Tuberculosis Sanitarium.

1. Wu: The Determination of Plasma Proteins, J. Biol. Chem. **51**:33 (March) 1922.

2. Bloor: Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227 (Feb.) 1916.

3. Sundstroem and Bloor: The Physiological Effects of Short Exposures to Low Pressures, J. Biol. Chem. **45**:153 (Dec.) 1920-1921.

the red cell count may be normal or even higher. This decrease in the corpuscle volume is due to a shrinkage in the size of the cell, a phenomenon which perhaps can be attributed to a disturbance in the osmotic pressure of the body fluids. The determination in the individual cell volume appears to depend on a loss in the water content rather than on the other constituents. As evidence, the phosphorus [4] content of the individual red cell in tuberculosis, although decreased in size, was found to be equal to or greater than that of the normal cell.

A definite disturbance in cholesterol metabolism occurs in tuberculosis. The cholesterol content of the blood may be either hyponormal or hypernormal. The increase may be attributed to one or more of the following factors:

The first is the immunization against infection. The relationship between cholesterol and immunity is probably due to the action of cholesterol against toxins as exhibited by the fact that hemolysis by saponin is prevented by cholesterol. The second is the need for

TABLE 1—*Average Normal Values*

	Percentage	Percentage
Corpuscle volume	45 (Men)	40 (Women)
Fibrin	0.300	±0.05
Albumin	4.900	±0.3
Globulin	2.200	±0.4
Albumin plus globulin	7.100	
Albumin / Globulin ratio, 2.2		
Cholesterol, 185 mg. per 100 cc.		

replenishing new cells lost through destruction of tissue, since cholesterol is a necessary constituent of all cells. The third factor is the destruction of cells, which liberates the cholesterol.[5] It is not excreted as a waste product, but is utilized for the formation of new cells.

A similar disturbance is expected in all tissues, associated with the disturbance in the blood cholesterol. Chauffard [6] found a definite equilibrium between the cholesterol content of the blood and the suprarenals in various diseases. The disturbance of the cholesterol in the tissues would modify the water content, since it has been shown that tissues with the most cholesterol have the greatest power of imbibing and holding water. Thus great emaciation and dehydration of body tissue (far advanced phthisis should show a hypocholesterolemia. This condition suggests a diet of food rich in cholesterol, such as eggs and

4. McCluskey: The Distribution of Phosphorus Compounds in the Blood in Tuberculosis, J. Lab. & Clin. Med. **10**:466 (March) 1925.

5. Dorée and Gardner: Proc. Roy. Soc., London, B, **81**: 109, 1908.

6. Chauffard, quoted by Shafer, E. Sharpley: Endocrine Organs, London, 1924, p. 109.

TABLE 2.—*Observations on Blood in Women with Pulmonary Tuberculosis*

Case	Date	Age	Corpuscle Volume, Percentage	Erythrocytes 10^6	Leukocytes 10^3	Hemoglobin, Tallqvist Test	Percentage of Fibrinogen	Percentage of Albumin	Percentage of Globulin	Total Percentage of Serum Proteins	Ratio of Albumin to Globulin	Cholesterol Mg. per 100 Cc.	National Tuberculosis Association Classification*	Comment
1	12/ 6/26	30	40.6	4.82	15.7	70	0.482	4.508	2.618	7.126	1.722	169.5	F.A.C.	Sputum positive; Wassermann negative; died 2/19/27 of Pott's disease
2	3/11/26	39	31.4	....	....	..	0.656	3.525	5.242	8.767	0.672	104.1	F.A.C.	Sputum positive; Wassermann negative; died 7/20/26
Average			36.0	....	....	..	0.569	4.016	3.930	7.946	1.197	136.8		
3	12/13/26	22	37.9	4.84	20.2	65	0.533	4.382	2.768	7.150	1.583	165.4	F.A.B.	Sputum positive; Wassermann negative
4	12/13/26	18	29.5	4.0	8.4	65	0.513	4.435	3.001	7.436	1.478	121.6	F.A.B.	Sputum positive; Wassermann negative; hemorrhage case
5	6/29/26	20	31.9	4.34	11.6	90	0.473	3.958	4.208	8.166	0.941	.....	F.A.B	Sputum positive; Wassermann negative; discharged 3/14/27; unimproved
6	10/ 4/26	17	30.8	4.72	14.5	70	0.620	4.352	2.707	7.089	1.619	153.1	F.A.B.	Sputum positive; Wassermann negative
7	9/23/26	24	33.4	5.0	15.6	70	0.637	4.720	2.547	7.267	1.853	161.8	F.A.B.	Sputum positive; Wassermann negative
8	9/23/26	21	30.7	4.0	10.9	..	0.556	4.365	2.810	7.175	1.556	167.6	F.A.B.	Sputum positive; Wassermann negative; ulcerative type; pneumothorax
9	7/29/26	27	39.0	4.28	11.4	70	0.443	4.183	4.163	8.346	1.028	158.4	F.A.B.	Sputum positive; Wassermann negative; ulcerative type
10	7/29/26	24	31.3	4.14	11.0	68	0.680	2.689	6.676	9.365	0.403	175.8	F.A.B.	Sputum positive; Wassermann negative; fluid in chest
11	8/ 2/26	21	32.0	4.63	8.9	65	0.479	5.365	2.797	8.162	1.198	200.9	F.A.B.	Sputum positive; Wassermann negative
12	8/ 6/26	32	29.0	4.43	14.5	70	0.547	4.846	3.394	8.240	1.428	181.4	F.A.B.	Sputum positive; Wassermann negative; died 8/25/26
13	4/ 8/27	34	42.6	3.9	10.7	70	0.538	4.680	3.306	7.986	1.416	193.6	F.A.B.	Sputum positive; Wassermann negative
14	9/20/26	32	37.7	5.03	14.1	..	0.533	4.583	3.142	7.725	1.459	177.2	F.A.B.	Sputum positive; Wassermann negative
15	9/14/26	21	29.6	3.75	12.6	55	0.512	4.583	3.002	7.585	1.527	.....	F.A.B.	Sputum positive; Wassermann negative
16	9/ 7/26	26	37.7	5.89	16.65	80	0.596	5.445	3.321	8.766	1.683	197.4	F.A.B.	Sputum positive; Wassermann negative; fibromyoma of uterus
17	9/14/26	18	38.8	5.48	14.0	85	0.493	5 340	3.507	8.847	1.523	180.0	F.A.B.	Sputum positive; Wassermann negative
18	4/18/27	27	41.0	....	....	..	0.602	4.380	3.820	8.200	1.147	162.2	F.A.B.	Sputum positve; Wassermann negative
19	8/17/26	22	32.7	3.65	14.5	85	0.443	5.528	3.244	8.772	1.704	193.6	F.A.B.	Sputum positive; Wassermann negative
20	3/13/26	31	....	....	....	..	0.630	3.304	3.910	7.214	0.845	.....	F.A.B.	Sputum positive; Wassermann negative; died 4/13/26
21	6/ 9/26	25	38.4	4.14	16.35	75	0.482	5.046	3.799	8.825	1.328	.....	F.A.B.	Sputum positive; Wassermann negative; under pneumothorax treatment
22	12/14/26	22	36.1	4.17	21.3	65	0.556	4.826	3.410	8.236	1.537	148.5	F.A.B.	Sputum positive; Wassermann negative
23	4/ 8/27	26	37.3	4.51	15.85	65	0.509	4.564	3.570	8.134	1.279	185.2	F.A.B.	Sputum positive; Wassermann negative
Average			34.35	....	....	..	0.542	4.553	3.480	8.033	1.320	172.1		
24	7/14/26	26	37.9	4.6	6.7	80	0.475	4.105	2.737	6.842	1.500	220.6	F.A.A.	Sputum positive; Wassermann negative
25	9/ 7/26	19	35.9	5.01	7.0	85	0.475	5.500	3.360	8.860	1.633	169.2	F.A.A.	Sputum positive; Wassermann negative
26	12/ 3/26	17	46.8	5.92	13.45	80	0.729	3.548	2.523	6.071	1.402	204.1	F.A.B.	Sputum positive; Wassermann negative; albumin in urine, 2 Gm. per day
27	10/13/26	31	36.3	3.92	25.0	60	0.525	5.419	3.298	8.717	1.643	168.6	F.A.A.	Sputum positive; Wassermann negative
28	9/16/26	21	33.3	4.89	11.3	75	0.586	4.955	3.588	8.543	1.384	175.0	F.A.A.	Sputum positive; Wassermann negative
29	9/20/26	42	36.0	5.64	10.2	..	0.443	4.762	2.905	7.667	1.639	189.1	F.A.B.	Sputum positive; Wassermann negative
30	12/16/26	25	42.0	4.59	9.5	70	0.418	4.783	2.218	7.001	2.157	181.8	F.A.A.	Sputum positive; Wassermann negative
Average			38.3	....	....	..	0.521	4.725	2.947	7.672	1.623	187.0		
31	12/16/26	17	38.4	4.98	11.4	70	0.400	4.527	2.819	7.346	1.606	157.9	M.A.B.	Sputum positive; Wassermann negative
32	10/28/26	18	34.1	5.3	9.1	..	0.394	4.846	3.007	7.853	1.611	130.3	M.A.B.	Sputum positive; Wassermann negative
33	9/30/26	14	33.3	4.1	7.1	..	0.643	4.783	2.649	7.432	1.806	177.8	M.A.B.	Sputum positive; Wassermann negative
Average			35.2	....	....	..	0.473	4.718	2.825	7.543	1.674	155.3		
34	11/23/26	23	38.9	4.45	12.0	75	0.565	4.489	2.758	7.247	1.628	170.4	M.A.A.	Sputum positive; Wassermann negative

* The National Tuberculosis Association classifies tuberculosis in three stages, "far advanced," "moderately advanced" and "minimal." Each stage is further divided into three graduations, A, B and C (severe symptoms).

TABLE 3.—*Observations on Blood in Women with Pulmonary Tuberculosis*

Case	Date	Age	Corpuscle Volume, Percentage	Erythrocytes 10^6	Leukocytes 10^3	Hemoglobin, Tallqvist Test	Percentage of Fibrinogen	Percentage of Albumin	Percentage of Globulin	Total Percentage of Serum Proteins	Ratio of Albumin to Globulin	Cholesterol Mg. per 100 Cc.	National Tuberculosis Association Classification	Comment
72	9/30/23	21	31.7	3.86	8.2	..	0.613	4.622	2.797	7.419	1.652	196.7	F.A.B.	Sputum positive; Wassermann negative
	12/13/23		40.7	4.55	9.85	70	0.360	4.933	3.039	7.972	1.624	206.4	F.A.B.	Sputum positive; empyemic fluid
73	5/15/26	30	35.2	....	....	..	0.468	3.928	7.207	11.135	0.433	.....	F.A.B.	Weight 102 pounds (46.3 Kg.); sputum positive; Wassermann negative
	7/26/26		36.0	5.18	13.3	75	0.497	3.971	4.115	8.085	0.965	255.7	F.A.B	
	12/29/26		38.8	5.46	12.25	68	0.443	5.641	2.583	8.224	2.184	194.8	F.A.A.	Discharged 12/31/26; improved
74	6/17/26	31	34.3	4.84	9.0	75	0.541	4.472	4.703	9.175	0.951	151.0	F.A.B.	Sputum positive; Wassermann negative
	3/14/27		39.3	5.0	14.9	60	0.505	4.200	3.355	7.555	1.252	197.0	F.A.A.	Discharged 4/14/27; improved
75	8/20/26	22	28.0	4.41	16.25	70	0.432	4.044	4.780	8.824	0.845	187.2	F.A.B.	Sputum positive; Wassermann negative
	4/ 1/27		31.7	4.76	11.45	60	0.410	4.321	2.610	6.931	1.621	204.0	F.A.A.	Sputum negative; clinically improved
76	8/ 2/26	14	39.4	4.33	12.60	80	0.547	4.825	3.931	8.756	1.227	169.1	F.A.B.	Sputum positive; Wassermann negative
	4/ 1/27		44.7	4.95	13.1	70	0.331	4.890	2.391	7.191	2.125	175.5	F.A.B.	Sputum negative; arrested
77	9/16/26	23	33.2	6.22	7.75	80	0.547	5.641	2.714	8.355	2.079	.....	M.A.B.	Sputum positive; Wassermann negative
	3/20/27		40.7	4.51	10.0	80	0.468	5.190	3.201	8.391	1.622	.....	M.A.A.	Sputum negative; discharged 3/20/27; apparently arrested
78	5/25/26	21	39.8	5.0	8.6	75	0.388	4.890	3.875	8.765	1.262	140.7	M.A.B.	Sputum positive; Wassermann negative
	2/10/27		46.8	5.1	8.2	70	0.328	5.092	1.713	6.805	2.972	216.3	M.A.B.	Discharged 4/14/27; improved; sputum negative
79	6/17/26	28	33.5	4.13	10.6	75	0.455	4.545	4.504	9.049	1.010	134.8	M.A.B.	Sputum positive; Wassermann negative; weight 115 pounds (52.1 Kg.)
	12/14/26		44.7	5.13	17.4	70	0.360	5.140	2.353	7.493	2.184	171.4	M.A.A.	Weight 118 pounds (53.5 Kg.); sputum negative; discharged 12/15/26; improved
80	6/29/23	19	35.8	4.27	13.0	70	0.258	4.603	3.895	8.498	1.182	.....	M.A.A.	Sputum positive; Wassermann negative
	10/13/26		39.4	4.49	12.0	75	0.368	4.933	2.910	7.843	1.695	157.9	M.A.A.	Discharged 10/13/26; quiescent
81	8/17/26	15	32.9	4.49	6.7	75	0.412	5.420	3.413	8.833	1.576	191.3	Min.A.	Weight 83 pounds (37.6 Kg.); sputum negative; Wassermann negative
	11/23/26		40.8	4.7	8.1	80	0.283	5.314	2.806	8.120	1.892	208.4	Min.A.	Clinical improvement
	12/14/26		38.7	5.53	11.8	75	0.301	5.092	2.635	7.727	1.932	172.4	Min.A.	Weight 98.5 pounds (44.7 Kg.); discharged 12/24/26

Case	Date	Age	Corpuscle Volume, Percentage	Erythrocytes 10^6	Leukocytes 10^3	Hemoglobin, Tallqvist Test	Percentage of Fibrinogen	Percentage of Albumin	Percentage of Globulin	Total Percentage of Serum Proteins	Ratio of Albumin to Globulin	Cholesterol Mg. per 100 Cc.	National Tuberculosis Association Classification	Comment
35	7/ 8/26	17	40.6	4.36	8.95	70	0.452	4.365	4.090	8.455	1.067	141.7	F.A.C.	Sputum positive; Wassermann negative; died 9/16/26
36	7/20/26	17	34.7	4.31	12.75	70	0.490	4.846	4.725	9.571	1.026	.....	F.A.C.	Sputum positive; Wassermann negative; discharged 9/1/26; bilateral cavities
37	2/ 4/26	28	34.0	4.07	15.85	65	0.609	2.997	5.244	8.241	0.572	.....	F.A.C.	Sputum positive; Wassermann negative; discharged 5/1/26; unimproved
38	6/22/26	28	31.4	4.11	16.65	65	0.604	4.074	4.665	8.739	0.873	106.1	F.A.C.	Sputum positive; Wassermann negative
39	8/31/26	23	33.6	5.00	18.55	75	0.508	5.444	2.768	8.212	1.957	191.0	F.A.C.	Sputum positive; Wassermann negative; acute exudative
40	10/ 4/26	26	36.2	4.70	16.4	..	0.686	4.489	3.157	7.646	1.4 2	163.0	F.A.C.	Sputum positive; Wassermann negative
41	12/ 3/26	20	44.5	5.96	16.55	75	0.580	4.783	3.029	7.812	1.579	172.5	F.A.C.	Sputum positive; Wassermann negative
42	3/18/27	40	42.7	4.91	15.75	75	0.493	4.30	3.679	7.679	1.087	159.0	F.A.C.	Sputum positive; Wassermann negative
							0.560	4.374	3.920	8.294	1.199	155.5		
Average.....			38.2	....	....	..	0.537	4.602	3.267	7.869	1.442	187.6	F.A.B.	Sputum positive; Wassermann A.C.; died 11/22/26
43	8/20/26	21	38.0	4.78	11.4	85	0.482	4.660	3.141	7.801	1.483	.....	F.A.B.	Sputum positive; Wassermann negative; tuberculous enteritis; died 3/25/27
44	8/ 6/26	27	....	5.33	17.1	65								
45	4/ 1/27	25	45.2	4.80	11.1	75	0.452	3.985	2.828	6.813	1.409	162.2	F.A.B.	Sputum positive; Wassermann negative
46	6/21/26	28	39.9	4.49	6.2	75	0.547	4.313	4.930	9.243	0.875	152.8	F.A.B.	Sputum negative; Wassermann 4 plus; pleuritic effusion
47	6/22/26	21	29.5	3.85	7.15	70	0.657	3.957	4.870	8.227	0.813	121.7	F.A.B.	Sputum positive; Wassermann negative; epididymitis; died 9/20/26
48	12/16/26	17	36.4	4.54	17.55	65	0.607	4.231	2.607	6.840	1.623	153.9	F.A.B.	Sputum positive; Wassermann 2 plus
49	5/17/26	22	31.2	4.46	17.85	60	0.490	3.395	5.051	8.446	0.672	.....	F.A.B.	Sputum positive; Wassermann 2 plus; discharged 10/6/26; quiescent
50	12/ 3/26	27	46.7	4.74	6.8	80	0.288	4.472	3.422	7.894	1 386	214.3	F.A.B.	Sputum positive; Wassermann negative
51	3/18/27	33	25.6	3.19	11.8	60	0.810	3.550	5.147	8.697	0.689	152 3	F.A.B.	Sputum positive; blood in urine
52	6/11/26	31	36.5	....	....	..	0.643	3.859	3.735	7.594	1.033	176.9	F.A.B.	Sputum positive; miliary tubercles on tongue; died 8/12/26
53	2/ 4/26	17	45.4	5.0	13.8	70	0.619	3.108	4.235	7.343	0.734	.....	F.A.B.	Sputum positive; Wassermann negative
							0.558	4.012	3.939	7.942	1.105	165.2		
Average.....			37.5	....	....	..	0.401	5.500	2.193	7.693	1.888	150.2	F.A.A.	Sputum positive; Wassermann negative
54	8/17/26	23	40.6	5.63	13.8	80	0.482	5.670	2.679	8.349	2.117	176.5	F.A.A.	Fibroid; sputum positive; Wassermann 4 plus
55	10/28/26	36	43.8	4.3	16.9	..	0.535	5.190	2.180	7.370	2.380	171.4	F.A.A.	Sputum positive; Wassermann negative
56	12/ 8/26	35	44.5	4.99	7.75	70	0.472	5.453	2.351	7.804	2.128	166.1		
Average.....			42.9	....	....	..	0.581	5.610	3.213	8.823	1.747	174.0	M.A.B.	Sputum positive; Wassermann negative
57	8/17/26	42	40.5	4.92	13.1	70	0.410	5.212	2.704	7.916	1.939	180.7	M.A.B.	Sputum positive; Wassermann negative; discharged 3/26/27; improved
58	11/ 4/26	20	35.9	5.53	15.1	75								
59	12/20/26	19	41.5	4.59	18.6	75	0.508	4.490	2.547	7.037	1.733	183.0	M.A.B.	Sputum positive; Wassermann negative
60	2/10/27	26	43.8	5.25	16.3	75	0.390	5.305	2.283	7.618	2.350	181.4	M.A.B.	Sputum positive; Wassermann negative
61	12/ 6/26	22	42.4	4.75	13.95	70	0.505	4.564	2.980	7.544	1.532	166.7	M.A.B.	Sputum positive; Wassermann negative; 4/1/26, M.A.A.
62	12/ 6/26	24	48.4	4.95	14.05	65	0.429	4.661	3.031	7.692	1.538	155.3	M.A.B.	Sputum positive; Wassermann negative; discharged 4/8/27; improved
63	7/ 6/26	23	41.3	4.72	5.3	85	0.458	4.955	4.254	9.209	1.165	165.5	M.A.B.	Sputum negative
64	3/18/27	18	37.5	4.22	12.95	65	0.556	3.831	3.553	7.384	1.078	115.2	M.A.B.	Sputum positive; Wassermann negative
65	3/18/27	33	44.2	5.31	10.15	75	0.521	4.910	2.873	7.783	1.719	158.0	M.A.B.	Sputum positive; Wassermann negative
Average.....			41.7	....	....	..	0.484	4.844	3.048	7.893	1.644	164.5		
66	12/ 3/26	31	44.4	5.15	15.85	70	0.407	5.445	3.553	8.998	1.532	192.7	M.A.A.	Sputum positive; Wassermann negative
67	2/20/26	33	35.4	4.75	19.52	65	0.643	3.350	4.095	7.440	0.819	.....	M.A.A.	Sputum positive; Wassermann negative; developed diarrhea; died 7/25/26
68	7/19/26	22	40.2	5.14	9.7	85	0.513	5.069	4.249	9.318	1.193	.....	M.A.A.	Sputum positive; Wassermann 4 plus
69	3/14/26	30	47.8	4.69	9.85	75	0.309	4.890	2.331	7.221	2.098	206.5	M.A.A.	Sputum positive; Wassermann negative
Average.....			41.9	....	....	..	0.470	4.688	3.556	8.244	1.410	199.6		
70	1/25/27	30	44.8	5.46	7.9	70	0.462	4.510	3.020	7.530	1.502	199.6	Min.A.	Sputum positive; Wassermann negative
71	7/20/26	34	47.9	4.87	8.7	85	0.269	5.820	2.422	8.242	2.403	192.3	Min.A.	Sputum negative; Wassermann negative; discharged 12/5/26; improved
Average.....			46.3	....	....	..	0.365	5.165	2.721	7.886	1 952	191.4		

TABLE 5.—*Observations on Blood in Men with Pulmonary Tuberculosis*

Case	Date	Age	Corpuscle Volume, Percentage	Erythrocytes 10^6	Leukocytes 10^3	Hemoglobin, Tallqvist Test	Percentage of Fibrinogen	Percentage of Albumin	Percentage of Globulin	Total Percentage of Serum Proteins	Ratio of Albumin to Globulin	Cholesterol Mg. per 100 Cc.	National Tuberculosis Association Classification	Comment
82	2/ 4/26	27	41.7	5.62	16.7	70	0.581	2.989	4.604	7.593	0.649	.....	F.A.C.	Sputum positive; Wassermann negative
	8/26/26		36.1	4.79	11.45	80	0.625	5.240	3.697	8.937	1.417	214.2	F.A.C.	Sputum positive; improved
83	2/20/26	20	46.5	4.78	13.3	75	0.631	2.920	4.920	7.840	0.593	.....	F.A.C.	Sputum positive; Wassermann negative
	8/12/26		36.3	4.67	15.05	80	0.468	5.092	2.521	7.613	2.019	237.0	F.A.B.	
84	4/26/26	32	42.0	....	....	..	0.643	3.469	6.831	10.300	0.508	101.8	F.A.C.	Sputum positive; Wassermann negative
	8/26/26		36.7	4.71	17.85	80	0.521	4.508	3.825	8.333	1.179	154.6	F.A.A.	
85	4/26/26	42	41.3	4.92	17.75	70	0.683	3.703	7.119	10.822	0.520	114.2	F.A.C.	Sputum positive; Wassermann negative
	8/31/26		43.2	5.74	13.25	85	0.586	4.661	3.950	8.611	1.181	185.0	F.A.A.	Discharged 12/2/26; improved
86	10/ 4/26	27	36.2	4.70	16.40	..	0.686	4.489	3.157	7.646	1.422	163.0	F.A.C.	Sputum positive; Wassermann negative
	2/10/27		35.6	4.10	18.15	65	0.607	4.331	3.404	7.735	1.273	164.2	F.A.C.	Some clinical improvement; laryngitis; sputum positive
87	6/10/26	44	45.4	4.87	16.25	75	0.461	3.928	3.886	7.814	1.011	177.0	F.A.B.	Sputum positive; Wassermann negative
	10/18/26		42.3	6.22	13.2	85	0.462	4.720	3.390	8.110	1.361	185.2	F.A.B.	Sputum positive; discharged 2/10/27; improved clinically
88	5/17/26	35	38.6	5.46	13.65	90	0.490	4.128	3.667	7.795	1.124	121.6	F.A.B.	Sputum positive; Wassermann negative; weight 144 pounds (65.3 Kg.)
	8/10/26		39.1	4.77	8.5	75	0.656	5.070	3.312	8.382	1.531	186.0	F.A.B.	Weight 122.5 pounds (55.5 Kg.); unimproved
	10/25/26		36.3	3.75	13.2	..	0.551	5.022	3.072	8.094	1.635	180.0	F.A.B.	Sputum positive; weight 133.5 pounds (60.5 Kg.); discharged 12/10/26; F.A.C.
89	5/20/26	23	38.4	5.11	22.6	70	0.656	4.365	4.309	8.764	0.992	126.6	F.A.B.	Sputum positive; Wassermann negative; weight 142 pounds (65.3 Kg.)
	4/12/27		48.1	5.35	9.45	80	0.405	5.117	3.355	8.472	1.526	150.0	F.A.A.	Sputum positive; discharged 9/25/26; quiescent
90	6/ 1/26	30	35.5	5.01	6.0	70	0.440	4.846	3.870	8.716	1.252	173.1	F.A.B.	Sputum positive; Wassermann negative
	10/18/26		43.8	5.45	7.05	80	0.426	5.980	2.555	8.535	2.340	185.1	F.A.A.	
91	7/ 6/26	18	39.5	4.65	13.4	..	0.446	5.445	3.228	8.673	1.687	165.6	F.A.B.	Sputum positive; Wassermann negative; active
	1/ 4/27		41.1	....	....	..	0.331	4.890	2.182	7.072	2.240	173.4	F.A.C.	Pneumothorax case; sputum positive
92	7/ 6/26	25	36.6	4.4	8.0	80	0.394	5.419	3.435	8.854	1.578	155.2	F.A.B.	Sputum negative; Wassermann negative; pleural effusion
	1/ 4/27		46.6	....	....	..	0.309	5.117	2.578	7.695	1.985	171.5	F.A.A.	Sputum negative
93	7/ 8/26	21	38.1	4.74	14.0	70	0.537	4.280	3.750	8.030	1.141	125.1	F.A.B.	Sputum positive; Wassermann negative
	12/20/26		42.8	5.28	13.1	75	0.497	4.762	2.415	7.177	1.972	146.1	F.A.A.	Sputum positive; discharged 12/22/26; improved

94	12/ 8/26	20	40.0	4.46	13.0	70	0.559	4.826	2.780	7.606	1.736	155.4	F.A.B.	Sputum positive; Wassermann negative; laryngitis
	2/10/27		32.4	3.92	12.95	60	0.388	3.227	2.778	6.005	0.860	130.8	F.A.C.	Died 2/18/27
95	6/ 4/26	27	43.4	4.21	13.0	..	0.455	4.331	3.987	8.318	1.086	244.5	F.A.A.	Sputum positive; Wassermann negative; gonorrhea
	10/26/26		40.7	....	....	..	0.350	5.789	2.867	8.656	2.018	236.8	F.A.A.	Sputum positive
96	7/16/26	25	38.3	5.19	9.35	80	0.375	4.527	4.345	8.873	1.042	171.8	F.A.A.	Sputum positive; Wassermann negative
	10/21/26		33.9	4.96	10.25	75	0.370	4.680	2.710	7.390	1.727	155.2	F.A.A.	Sputum positive
97	7/16/26	40	38.5	4.82	11.45	80	0.509	4.365	4.305	8.670	1.014	175.8	F.A.A	Sputum positive; Wassermann negative
	10/21/26		37.9	4.1	16.4	..	0.465	4.450	3.085	7.535	1.443	182.9	F.A.B.	Sputum positive
98	7/16/26	45	37.3	4.34	10.35	85	0.525	4.264	2.873	7.133	1.485	267.9	F.A.A.	Sputum positive; Wassermann negative
	11/ 4/26		44.8	5.11	9.2	80	0.410	5.274	2.402	7.676	2.197	202.8	F.A.A.	Sputum positive; Improvement
99	7/14/26	23	43.2	5.32	8.15	80	0.547	4.215	3.041	7.256	1.387	190.6	M.A.B.	Sputum positive; Wassermann negative
	11/23/26		43.3	4.82	13.6	80	0.542	5.023	2.394	7.417	2.098	173.1	M.A.B.	Sputum positive; discharged 11/26/26
100	7/16/26	30	34.8	4.46	12.6	80	0.452	4.400	4.861	9.251	0.905	222.8	M.A.B.	Sputum positive; Wassermann negative
	3/14/27		45.5	4.6	8.75	70	0.526	4.681	2.742	7.423	1.707	208.0	M.A.A	Sputum positive; marked improvement
101	9/27/26	23	46.4	4.81	13.25	75	0.542	4.805	3.160	7.965	1.520	176.5	M.A.B.	Sputum positive; Wassermann negative
	4/ 4/27		50.0	5.80	12.56	75	0.465	4.583	2.401	6.984	1.910	159.5	M.A.B.	Sputum positive; Wassermann negative
102	10/ 4/26	29	37.3	4.40	9.8	80	0.458	5.167	2.216	7.383	2.279	236.9	M.A.B.	Sputum positive; Wassermann negative
	4/ 6/27		43.1	5.07	13.8	80	0.455	4.838	2.606	7.474	1.868	192.3	M.A.A.	Sputum negative
103	8/12/26	27	30.5	3.86	7.05	80	0.547	4.846	2.895	7.741	1.674	261.7	M.A.C.	Sputum positive; Wassermann negative; adenitis
	12/13/26		40.2	5.17	6.5	80	0.493	5.070	2.807	7.877	1.806	187.5	M.A.A.	Discharged 9/10/26; quiescent
104	12/ 8/26	30	51.3	5.32	17.35	80	0.537	4.826	3.060	7.886	1.577	172.4	M.A.B.	Sputum positive; Wassermann negative
	4/ 6/27		51.0	6.53	12.2	90	0.375	4.933	2.417	7.350	2.042	192.0	M.A.A.	Discharged 4/9/27; improved
105	10/28/26	40	35.8	5.33	11.1	80	0.575	4.365	3.304	7.669	1.321	.....	M.A.A	Sputum positive; Wassermann negative
	4/ 4/27		42.2	5.8	16.02	70	0.656	3.956	3.183	7.142	1.242	176.5	Min.B.	Sputum positive
106	11/ 4/26	23	43.5	4.85	14.1	70	0.497	4.680	3.196	7.876	1.464	174.4	M.A.A.	Sputum positive; Wassermann negative
	4/ 4/27		36.2	5.37	15.02	75	0.432	4.680	2.401	7.081	1.950	158.0	M.A.A.	Sputum negative
107	6/ 4/26	23	41.5	5.08	14.3	70	0.410	4.847	3.960	8.807	1.289	161.5	M.A.A.	Sputum positive; Wassermann negative; weight 145 pounds (65.8 Kg.)
	10/21/26		39.6	4.51	10.7	70	0.362	4.720	2.805	7.525	1.677	193.9	M.A.A.	Sputum negative; discharged 12/11/26; quiescent
108	9/27/26	20	41.9	5.3	9.2	..	0.402	5.190	1.975	7.165	2.628	172.4	Min.B.	Sputum positive; Wassermann negative
	2/17/27		46.1	5.33	8.7	78	0.298	4.846	2.495	7.341	1.942	193.9	Min.A.	Sputum negative; discharged 2/26/27; arrested
109	8/24/26	21	44.2	5.23	9.7	80	0.443	5.500	2.333	7.833	2.357	300.0	Min.B.	Sputum positive; Wassermann negative
	4/ 6/27		48.1	5.55	11.7	77	0.469	5.365	2.283	7.648	2.350	263.1	Min.B.	Sputum negative; quiescent

butter, since the level of cholesterol in the blood and likewise in the tissues can be raised through the feeding of cholesterol or foods rich in cholesterol.

CONCLUSIONS

The data given in the tables justify the following conclusions: First, with a subnormal cholesterol content, clinical improvement is accompanied by an increase in blood cholesterol (table 5, patients 84, 85, 88, 89, 93 and 104), while the reverse can be observed in patients 94 and 96 (table 5). Second, a stationary or increasing hypercholesterolemia in tuberculosis indicates immunity and resistance, and a falling hypercholesterolemia indicates the opposite.

Fibrin, a plasma globulin, is a labile substance compared with the other blood proteins. Since it reacts to a multitude of stimuli within the body, an individual fluctuation of from 20 to 25 per cent is considered within normal limits. The only factors that have been proved to influence fibrin content are food, hemorrhage, inflammation, injury to tissue and certain general intoxications which do not cause any obvious injury to cells. The increase in fibrin found in tuberculosis may be due to injured tissue, to the familiar inflammation which usually accompanies extensive tissue injury and to the presence of pathogenic organisms, although Foster and Whipple[7] conclude that bacteria are not directly concerned in this reaction, since fibrin values are identical in blood whether a sterile or a septic inflammation is present. This conclusion seems to account for the results obtained from a comparison of the fibrin values and the leukocyte count; namely, all patients with a high leukocyte count have a high fibrin value (table 2, patients 16, 3, 10, 27, 14), but the high leukocyte count does not in all instances accompany a high fibrin (table 2, patients 24, 25, 33; table 4, patients 46, 47, 56). Since injury to tissue is the most powerful single stimulus to the overproduction of fibrinogen in the blood, it follows that the quantity of fibrinogen is a direct measure of the amount of tissue undergoing active destruction. This accounts for the fact that often fibrinogen is as high in the moderately advanced or incipient type of tuberculosis as in the far advanced cases.

Serum proteins under ordinary conditions in the individual case are relatively constant, but may vary, particularly in disease. A disturbance in the concentration of the albumin and the globulin occurs in tuberculosis—a condition which is difficult to explain, since little is known of the exact function of the proteins in the blood.

The fluctuations of serum proteins in tuberculosis were found to be an increase in the globulin fraction with a decrease in the albumin

7. Foster and Whipple: Blood Fibrin Studies, Am. J. Physiol. **58**:408 (Jan.) 1922.

in the majority of cases, and a normal or slightly increased total protein, especially in the far advanced type. The increase in globulin may be due to the body's resistance to infection, to formation of toxins, or to a development of immune bodies. Moll [8] found a similar increase in globulin in animals injected with various proteins, gelatin and killed bacteria. The usual decrease in the albumin may be partially the result of the body's attempt to reduce the osmotic pressure of the blood. Additional factors evidently are involved; otherwise the albumin would decrease more than has been observed in order to equalize the increase in the osmotic pressure caused by the increase in globulin. The percentage increase in globulin is about six times the percentage decrease in albumin, although the globulin molecule is approximately only twice the molecular weight of the albumin molecule.

The fluctuation in the total protein content cannot be ascribed alone to changes in the water content of the blood and tissues, since the changes in the individual fractions are not simultaneous. The usual sequence is an increase in fibrinogen, later an increase in globulin, followed by a decrease in albumin. These changes represent true alterations in the protein content and are not the result of simple fluctuations in the water content, although any disturbance in the water balance must have its effect on the concentration of the constituents of the blood.

SUMMARY

Chemical studies in tuberculosis demonstrated the following facts:

1. The cell volume is usually below normal, especially in active cases with much emaciation.

2. The size of the erythrocyte is decreased.

3. The cholesterol content of the blood may be increased or decreased.

4. A rising or stationary hypercholesterolemia indicates resistance and immunity, while a falling hypercholesterolemia or a hypocholesterolemia represents a lowering in resistance and immunity.

5. Fibrinogen is increased in proportion to the amount of tissue undergoing destruction.

6. The globulin values are definitely increased, associated with a smaller percentage decrease in the albumin.

7. The total serum proteins are normal or hypernormal, the increase being due to the high fraction of globulin.

8. Moll: Beitr. z. Chem. Phys. u. Path. **4**:563, 1903.

POSTURAL TREATMENT OF LUNG SUPPURATION

A NEW POSTURAL FRAME, THE JACK-KNIFE POSITION AND ABDOMINO-DIAPHRAGMATIC PULMONARY COMPRESSION, WITH A REVIEW OF THE LITERATURE *

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Postural treatment, though recognized as decidedly valuable in pulmonary suppurative conditions, has not received the attention it deserves. Considering its importance, it is surprising that not only clinicians, but also bronchoscopists and thoracic surgeons have not taken advantage of and put into more general use a procedure having merited value.

Considering the possession of the knowledge by primitive peoples of the value of the use of the upside-down position for emptying the lungs of inspired water in cases of drowning, as well as the more modern methods of Marshall Hall, Sylvester, Howard and Schaefer, it is surprising that the scientific and practical value of posture for evacuating purulent accumulations in the lungs was not commonly recognized until about twenty-five years ago. It is difficult to understand that it was not until the decade just passed that the principle of postural drainage for lung suppuration began to find advocates and the knowledge of its value became popularized.

REVIEW OF LITERATURE

A search of the literature reveals a strikingly small number of articles on this subject. Only a few of these are devoted exclusively to the description, consideration and advocacy of postural methods; several authors cite cases in which patients were cured by this means, while others simply quote case reports with results obtained, or casually mention the value of posture as an additional aid in the treatment of patients with suppurative conditions of the lungs. With few exceptions, textbooks are silent on this mode of treatment; some merely mention it in passing and do not give a description of the method or the manner of application.

That pulmonary suppuration was not unknown in antiquity is evidenced by mention by Hedblom [1] of the teaching of that wise old masterphysician, Hippocrates (quoted by Koch), who demonstrated that a pulmonary abscess that had burst into the pleural cavity could be healed

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1. Hedbloom, C. A.: Pulmonary Suppuration, M. Rec. **96**:442 (Sept. 13) 1919.

by draining the latter. It was Laennec,[2] however, who first placed pulmonary disease on a reliable basis, and who differentiated bronchiectasis (first noted by his assistant Cayol in 1808), pneumothorax, hemorrhagic pleurisy, gangrene and emphysema of the lungs, esophagitis and chronic diffuse interstitial hepatitis.

In 1898, von Quincke (according to Schaefer [3]) was the first to treat patients who had bronchiectasis by using the oblique position, and to him, apparently, belongs the credit of first placing the treatment for pulmonary suppurative conditions by postural methods on a scientific basis.

A cure of abscess of the lung by postural treatment was reported in 1912 by McKechnie.[4] He reported the case of a boy, aged 14. The diagnosis was abscess of the liver, with perforation of the diaphragm and pleura and secondary abscess at the base of the lung. If this condition were present, there was little hope that the cavities could be healed under ordinary circumstances. The boy was suspended over the edge of a table, head downward, the whole body hanging vertically upside down, the legs and thighs lying on the table at right angles to the body and thus supporting him. In this position he was made to cough and to squeeze the chest until no more pus came out. The process was repeated five or six times daily, and by this means the abscess cavity was completely emptied. Progress was remarkable; in six weeks the boy was cured without operation of a condition which had lasted five years, and which had baffled other modes of treatment. McKechnie advocated the use of this method before recourse is made to surgery.

In 1913, Garre and von Quincke [5] stated that in the case of cavities in the lower lobe, expectoration is furthered most effectually by the patient's lying flat or with the shoulders at a lower level (several times a day from one to three hours; the morning hours are the best—from 5 to 9 or from 6 to 9—and in the evening from 5 to 7); in other cases tests must be made to find the most suitable position.

In 1915, Lord [6] stated that the effect of posture should invariably be given a thorough trial. Evacuation may be favored if the patient lowers his head over the edge of the bed during a paroxysm of coughing. At stated intervals for a certain period the patient should lie with the affected side uppermost for the purpose of draining the pus into the

2. Laennec: Garrison's History of Medicine, 1921.

3. Schaefer, H.: Postural Treatment of Bronchial Disease, Klin. Wchnschr. **2**:252 (Feb. 5) 1923; J. A. M. A. **80**:1493 (May 19) 1923.

4. McKechnie, W. E.: Abscess of the Lung and Liver. Simple Cure of a Chronic Case by the Upside-Down Position, Lancet **1**:865 (March 30) 1912.

5. Garre and von Quincke: Treatment of Pulmonary Suppurations. Translated by D. M. Barcroft, Ed. 2., New York, William Wood & Company, 1913.

6. Lord, Frederick Taylor: Empyema and Pulmonary Abscess, Boston M. & S. J. **173**:798, 1915.

trachea. Elevation of the foot of the bed for a time night and morning, with the patient lying at full length on the back or abdomen, and without a pillow, should be tried.

DeJong,[7] in 1918, reported a case of bronchiectasis of several months' standing. The cough was distressing and the sputum was extremely malodorous, but no tubercle bacilli were found. One lung seemed normal, but the temperature remained subfebrile. The man was in the hospital for nearly four months; he steadily grew weaker, and there seemed to be no hope that an operation could be performed. Then deJong raised the foot of the bed 40 cm., and administered potassium iodide freely. At first this slanting position was maintained only one hour in each four, but the benefit was so prompt and so marked that the man begged to have the bed kept slanting all the time. The expectoration diminished, the cough subsided and in seven weeks the man left for his farm, his health completely restored. One young girl given similar treatment was in robust health several years later. The iodide and copious drinking diluted the sputum, and the sloping position ensured its expulsion. The position treatment should be given a trial first. Zaaijer (quoted by deJong) has reported a case in which a young woman with bronchiectasis happened incidentally to discover the relief from lying with the shoulders low, and she spontaneously assumed this position every morning.

In 1919, Hedblom,[1] in an article to which is appended a complete bibliography on lung suppuration, mentioned that patients often discover that certain positions favor expectoration and unconsciously make use of gravity to help empty the cavity. That spontaneous cures occur in this manner is to be expected. He also stated that patients have been cured even of abscesses perforating from the liver by promoting gravity drainage (quoting McKechnie's[4] case). Recently, von Deeston[8] reported a similar case in which a perinephritic abscess ruptured into a bronchus. Patients with acute cases of a mild type may be treated expectantly for a few weeks in the hope that drainage through a bronchus may effect a cure. The mortality following expectant treatment at first was high.

Wessler[9] also, in 1919, while recognizing the value of postural drainage, did not believe it exerted a curative effect. At that time, he wrote that "the *medical* treatment for suppurative disease of the lung offers little that is encouraging." He believed that constant violent coughing,

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7. DeJong, H.: Treatment of Bronchiestasia, Nederl. Tijdschr. v. Geneesk. **1**:495 (Feb. 16) 1918; abstr., J. A. M. A. **70**:1343 (May 4) 1918.

8. Von Deesten, H. T.: Recumbent Posture Cough with Purulent Expectoration, J. A. M. A. **88**:98 (Jan. 8) 1927.

9. Wessler, Harry: Suppuration of the Lung. A Study of 100 Cases, J. A. M. A. **73**:1818 (Dec. 27) 1919.

by projecting the infectious material farther down into the smaller bronchi, undoubtedly disseminated the disease, and promoted the formation of bronchiectasis. He also said, however, that periodic upsetting of the patients will facilitate drainage, and irrigation of the bronchi through the bronchoscope accomplishes the same purpose. He thought, however, that this procedure cannot cure these patients, as it does not have any effect on the pulmonary infiltration. (This contention, however, has recently been disproved by repeated physical examinations and roentgenograms of many patients treated by postural means over a long period.)

Of course, there are many chronic cases of long duration in which extensive fibrosis and other infiltrative changes have taken place that neither postural nor any other form of treatment will influence. The early institution of postural treatment plus all other properly selected and applied means will prevent the formation and aid resolution of considerable peribronchial infiltration and early fibrosis.

In 1920, Lehmann [10] advocated the use of the postural method, stating that the suspension method aided by procuring better drainage. In 1922, Carmody [11] advocated rest in bed for patients suffering from pulmonary suppuration with the foot of the bed elevated for postural treatment.

In 1922, Graham and Singer [12] advocated postural drainage as a method that often relieves a great many of the distressing symptoms by allowing large quantities of discharge at one time. This, of course, leaves the patient free from symptoms for hours at a time, and occasionally is sufficient to cause symptomatic cure. It was their impression that at best it is only a palliative method.

In 1923, Lukens, Moore and Funk [13] in an article on bronchoscopic treatment of lung suppuration, stated that in addition to bronchoscopic drainage, the best possible natural drainage can be secured by having the patient sleep on the "well" side and assume this position as much as possible during the day.

Schaefer [14] again reported the use of postural treatment in bronchial disease during the previous year. He used von Quincke's method in eleven cases, those of seven men and four women, with the most satisfactory results.

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10. Lehmann, J. E.: Lung Abscess, Canad. M. A. J. **10**:1090 (Dec.) 1920.
11. Carmody: Suppurative Conditions of Lung, New York M. J. **15**:742 (June 21) 1922.
12. Graham, E. A., and Singer, J. J.: New Treatments of Bronchiectasis, J. Missouri M. A. **19**:390 (Sept.) 1922.
13. Lukens, R. M., Moore, W. F., and Funk, E. H.: Bronchioscopic Drainage of Pulmonary Abscesses and Bronchiectasis, M. Clin. N. Amer. **6**:1015 (Jan.) 1923.
14. Schaefer, H.: Presse méd. **3**:109 (Feb. 3) 1923.

Whittemore [15] also prefers to give each patient a chance to cure himself by postural drainage and by building up his general condition before operation is advised.

In 1924, Lambert and Miller [16] advocated postural treatment for abscess of the lung. Their method consists of rest and postural drainage, the latter carried out four or five times daily for periods varying from five to twenty minutes each. Postural drainage is carried out by the patient hanging over the side of the bed with the head to the floor. This position is maintained from three to five minutes at first; as the patient becomes accustomed to it, the time is increased to as long as may be necessary to empty the abscess cavity thoroughly, usually from ten to fifteen minutes for each drainage. By this method it is possible to increase materially the number of cures by spontaneous drainage through a bronchus. Medical treatment for from three to four weeks can usually be safely employed to determine the necessity for operation.

In 1924, Moore,[17] after outlining the technic of bronchoscopic treatment for suppurative disease of the lungs said: "These patients are carefully instructed to aid, by posture, the drainage of the affected area."

In 1924, Weinberger [18] reported a remarkable improvement in the condition of a girl with bronchiectasis. An artificial pneumothorax made the situation worse. The successful outcome is attributed to von Quincke's slanting position used gradually for several hours daily.

In the same year, Mackey [19] reported complete recovery by postural drainage of a large abscess of the lung without surgical intervention.

In 1924, Dorendorf [20] observed spontaneous recovery in nineteen of his thirty-one cases of abscess of the lungs after influenza; nine patients, four of whom died, required an operation. Three of the other cases ended fatally. He attributes his nineteen cures to simple treatment: von Quincke's advice of a posture which facilitates evacuation of the pus, and restriction of fluid intake.

In 1926, Castlen [21] advocated the early institution of postural drainage for abscess of the lung by elevation of the foot of the bed or hips, or by the use of a special table, before resorting to more radical measures.

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15. Whittemore: Treatment of Non-tuberculous Pulmonary Abscess, Boston M. & S. J. **188**:477 (April 5) 1923.
16. Lambert, Adrian, V. S., and Miller, James Alexander: Abscess of Lung, Arch. Surg. **8**:446 (Jan.) 1924.
17. Moore, W. Frederick: The Bronchoscopic Treatment of Suppurative Disease of the Lungs, J. A. M. A. **82**:1036 (March 29) 1924.
18. Weinberger, R.: Bronchiectasis, Wien klin. Wchnschr. **37**:1067 (Oct. 9) 1924.
19. Mackey: International Medical & Surgical Survey (Med. 1066, Nor.) 1924.
20. Dorendorf, H.: Influenza and Lung Abscess, Med. Klin. **20**:1233 (Sept. 7) 1924.
21. Castlen, C. R.: Pulmonary Abscess, Northwest Med. **25**:294 (June) 1926.

In a recent article, Lambert [22] stated that "the crux of the successful treatment of lung abscess may be summed up by the one word 'drainage,' and in the management of any given case the problem is to effect adequate drainage." He also emphasized that 50 per cent of all patients recovered completely under the more conservative forms of treatment without operation.

Miller,[23] while speaking of abscess of the lung said:

> The primary and basic treatment is absolute bed rest combined with postural drainage. . . . This combination of rest and postural drainage constitutes, therefore, our basic method of treatment, to be first used in practically all cases, and the result obtained affords a point of approach to the consideration of additional methods which may be necessary. In our experience about twenty per cent of all cases are cured by these methods alone.

His description of the use of postural drainage is one of the best written thus far and should be read in the entirety by those interested in this method of treatment.

Since 1924, however, most of the writers previously quoted in subsequent articles and many surgeons who specialize in operations on the lungs mention the efficacy of postural treatment in pulmonary suppurative conditions, and advocate its trial preliminary to operative intervention.

This completes a rather careful survey of the literature. No doubt many cases in which the patients were cured by postural drainage have not been reported, and many more patients whose cases were unrecognized have been cured by spontaneous evacuation, postural or otherwise. Thus I believe sufficient evidence of the value of postural drainage in pulmonary suppuration has been adduced by reliable workers in this field.

METHODS AND APPARATUS USED IN TREATMENT

It has frequently been noted that patients suffering from conditions of this kind accidently discover that certain positions materially aid in ridding them of excessive accumulations of bronchial pus.

A prime requisite for gravitational relief is a nonobstructed outlet from the region of the abscess; hence it is obvious that the theoretically ideal position for postural drainage would be a suspension of the patient by the heels with the head hanging down and with the body hanging in a straight line with the feet uppermost—standing on one's head, so to speak. The impracticability of such a posture precludes the use of this method.

Up to the present time, the von Quincke position has been considered the best possible means of postural drainage applicable to the average case.

22. Lambert, Adrian V. S.: Pulmonary Abscess and the Treatment from the Surgical Standpoint, New York State J. Med. **27**:47 (Jan. 15) 1927.

23. Miller, James Alexander: Medical Aspects of Abscess of the Lung, New York State J. Med. **27**:43 (Jan. 15) 1927.

The method of having the patient lie flat on the abdomen with his chest over the edge of the bed and his head hanging low, at best serves as a makeshift, the pressure of the body against the bed precluding free respiration by creating obstructive pressure against the sternum and ribs as well as preventing free play of the intercostal, diaphragmatic and abdominal muscles.

The Jack-Knife Position.—An intensive study of the inverted body position in order to determine what posture would allow a low hanging head and at the same time a free play of the respiratory muscles led to the adoption of what I have called the "jack-knife position," so-called because of its resemblance to a half-closed pocket knife. In order to permit an easy assumption of this posture and a prolonged period of suspension with the head low, it was found that having the patient hanging on a band across the groins, the body flexed forward on the thighs, and the head at the most dependent position, approached the ideal, as thus the chest and abdominal muscles are free from pressure and an "inverted bronchial tree" is created, the ideal position for drainage.

Postural Frame for Body Suspension.—To permit the patient to assume and maintain this position easily and safely, I had a body suspension frame constructed (fig. 1). It consists of two U-shaped bent-pipe frames held together at their uppermost free ends by hinge-joints. Stretched horizontally between the upper joined ends of the frames is a stout chain covered with padded leather, across which one may hang at the groins with comfort. To prevent the side members from spreading from the weight of the body, a side bar is hooked from one side to the other.

Description of Use of Apparatus.—On the floor directly under the patient's head a basin is placed to receive the expectorated secretions. The patient is instructed to assume the jack-knife position immediately on arising in the morning and before retiring at night. He remains in the suspended position for from fifteen to twenty minutes at each seance, hanging with head suspended for three minutes and standing upright for one minute, to relieve him from dizziness or other unpleasant sensations that might arise from the blood rushing to his head or from the unaccustomed position.

During the first few days it is best to have him remain suspended with the head low for one minute periods, with two minute intervals of the upright position. Patients quickly become used to the posture, and the relief afforded makes them cooperate readily.

If when the patient assumes this position the secretions are not readily coughed out, he is instructed to cough a few times. This usually suffices to stimulate the cough reflex, and the retained secretions are ejected.

Abdominodiaphragmatic Pulmonary Compression.—Of additional value in aiding the patient to empty the purulent secretions, and possible only in the jack-knife position, is "abdominodiaphragmatic pulmonary compression." This is accomplished as follows: After the patient has evacuated as much secretion as possible by coughing, and while he is still in the suspended position (fig. 4), the physician stands behind the patient and (fig. 2) places his hands on the back of the patient's thighs near the popliteal regions, and a nurse, who stands in front of the patient, takes hold of his shoulders. The patient's body is then brought up into a nearly horizontal position (straightened out, fig. 2). He is then told to take a slow deep inspiration and to hold his breath; then the physician and attendent simultaneously push toward each other, bringing the patient's knees toward his chin and flexing the body as one would close a pocket knife (fig. 3); this is done in a firm quick manner. The muscles of the patient's abdomen become fixed, as does the diaphragm, and the forced flexion of the inflated chest on the thighs causes the diaphragm to press upward against the distended lungs, and whatever residual secretion remains in the lungs is readily expelled. This procedure is repeated once or twice during the first few treatments, and as the patient becomes accustomed to it, it may be repeated from six to eight times at each seance. In no other way can the lungs be so completely and efficiently emptied of retained purulent secretion.

CONCLUSION

As with abscesses in other regions, the prognosis of abscess of lung depends mainly on the freedom with which the purulent accumulation can evacuate itself. The less often and the less complete the evacuation of pus, the longer the duration of the disease process and the less chance for a complete recovery either by natural (nonsurgical) means or by induced methods (surgical intervention).

The marvelous recuperative properties of the bronchopulmonary mucosa, as well as the healing powers of the pulmonary tissues themselves, are known to all. When the load is taken off the overwhelmed mucosal cilia, if they have not been completely destroyed, and when mechanical obstructions, such as granulations and cicatrices, do not mechanically constrict the bronchial canals, resolution takes place with astonishing rapidity. Should any of the latter complications be present, they should receive the proper bronchoscopic attention.

The frequent dramatic cures of abscess of the lung following spontaneous evacuation by way of the normal air passages are familiar to all clinicians. These desirable results are not limited to solitary abscess of the lung, but are obtained also in cases of multiple bronchiectatic abscesses. The percentage of spontaneous cures of solitary pulmonary accumulation of pus is considerably greater than the multiple or

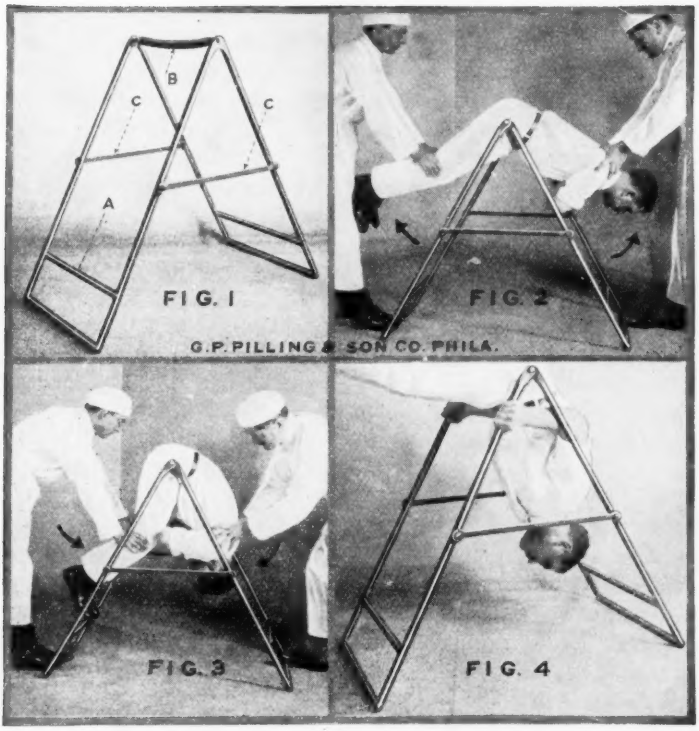

Fig. 1.—Postural body suspension frame for jack-knife position. *A* indicates the metal step, *B*, the padded leather-covered chain and *C*, the metal side bars.

Fig. 2.—The patient in extended position. Note inflated chest and position of attendants' grasp. The patient's body is carried upward in direction indicated by arrows.

Fig. 3.—The patient in flexed (jack-knife) position. After the body is brought into the position shown in figure 2, is told to take a deep breath and to hold it. The body is then suddenly and somewhat forcibly flexed into the position indicated by the direction of arrows.

Fig. 4.—The patient exercising without attendants. Note the position of the limbs. The patient brings thighs and legs downward flexing same on body. With the chest inflated with air, the mouth open, and holding the breath, the jack-knife position is assumed in a rather forcible manner. The sudden pressure of the diaphragm in the act of expiration forcibly exerts a sudden expulsive force by compressing the lungs and with the patient in the inverted posture, permits evacuation of a greater amount of bronchial secretion than any other postural means.

bronchiectatic form. The earlier the diagnosis is made and the sooner proper therapeutic measures are undertaken, the greater the possibility of an earlier and nonsurgical cure. In a considerable proportion of cases the condition resists every form of nonsurgical treatment, and despite medicinal, dietetic (restriction of fluids), vaccinal, climatic, bronchoscopic (irrigation and suction) and endoscopic treatment (topical application or injection of the various medicaments used in these cases) and the early institution of postural treatment, the patients gradually become worse, and unless radical and at times even heroic measures are instituted, a fatal termination ensues. Patients with pulmonary suppurative conditions cannot be treated by "rule of thumb" methods. Each case must be individualized, and the patient treated according to its peculiar type.

I wish to emphasize the importance of the early recognition and correct diagnosis of pulmonary suppuration. It is astonishing how many cases are unrecognized even in well conducted clinics until the simpler methods of treatment are of no value.

The curative value of postural treatment for pulmonary suppurative conditions depends on its early institution. In general, it might be stated that the earlier postural treatment is instituted, the greater is the chance for nonsurgical cure; however, I do not wish to have it understood that I contend that postural treatment alone will accomplish a large percentage of cures. True, a small number of cures will occur by spontaneous evacuation through the normal air passages and a larger number by spontaneous evacuation plus postural treatment; just so, postural treatment plus all the other aids properly selected and properly applied at proper times will permit a still greater percentage of cures. The patient who does not obtain some relief by postural treatment is exceptional.

I believe that bronchoscopic study and the various bronchoscopic treatments take first rank among the nonsurgical means thus far devised for the expectant treatment of suppuration of the lung. Reference here is made, of course, to those cases in which the patient is not moribund, or which are not strictly surgical cases. There are, however, many so-called borderline cases which, though serious, occasionally escape the more radical thoracoplastic surgical procedures by postural and bronchoscopic treatment.

Postural Treatment and Bronchoscopic Irrigation.—Postural treatment may be used without bronchoscopic irrigation, or if one favors the latter procedure for treatment in certain cases of pulmonary suppuration, it is of special value. If postural treatment is used before the bronchoscope is introduced, a considerable amount of the purulent material will be ejected; as a result, a smaller amount of irrigating fluid may be used, and it almost immediately comes in contact with the mucosa of the soiled but patent bronchi.

Again, postural treatment may be used to advantage after bronchoscopic irrigation. Following bronchoscopic irrigation and suction treatment for pulmonary suppuration, considerable free fluid remains in the bronchi, as is shown by the coughing and expectoration of varying amounts of an admixture of irrigating fluid, mucus, pus and often blood directly after such treatment. The utilization of the postural method immediately after the irrigation, and particularly the "jack-knife position," will enable the patient to free himself more easily and more completely from such residual fluids than would otherwise be possible.

Postural Drainage in Roentgen-Ray Study of Bronchiectasis.—Recently Singer and Graham[24] advised that postural drainage be instituted in bronchiectatic cases after the first roentgenogram is taken. They stated that subsequent roentgenograms will give information concerning the relative size of the bronchiectatic area.

Postural treatment, like many other means advocated for the relief or cure of certain conditions, because of improper use or improper instruction in its use is condemned as of little or no value. For the best results, the postural treatment for drainage of pulmonary suppuration must be applied according to the special requirements of the case. The same manner of application, frequency and length of treatment will not do for every case.

Many patients discover certain positions, movements and exercises while in the jack-knife position that enable them to empty their bronchial tree more easily than by those described. They should be permitted to utilize these exercises when not too strenuous or injurious, in preference to the routine measures. If assistance is not available at home, the patient can be taught to practice the procedure alone. Daily exercises are a sine qua non for the best possible results from postural treatment; these should be taken morning and night when possible; if once a day only, experiment will teach the patient the best hour. My patients are encouraged to purchase the apparatus for home use when their means permit. Members of their families can easily be taught to apply the abdominodiaphragmatic pulmonary compression method.

Respiratory gymnastics in the treatment of pulmonary suppuration is gradually assuming the important position in our armamentaria that it deserves. Arguments against it because of danger of inducing extension of the disease by auto-infection by inspiration of infective material fails to hold ground in the light of recent investigations. The extension of "draining" or "drainable" abscess of the lung, simple or bronchiectatic, is limitable to the primarily affected areas, once drainage is established either by postural or by surgical means.

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24. Singer, J. J., and Graham, E. A.: Roentgen-Ray Study of Bronchiectasis, Am. J. Roentgenol. **15**:54 (Jan.) 1926.

CLINICAL RESULTS WITH EPHEDRINE THERAPY

A REPORT OF SIXTY-TWO CASES *

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AND
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SAN FRANCISCO

Ephedrine is an alkaloid that was isolated from the plant *Ephedra vulgaris* by Nagai in 1887 and rediscovered by Chen in 1923. Decoctions of *Ephedra vulgaris* have been used in China for five thousand years for diaphoretic and antipyretic purposes and as a sedative in cough. At the time of the original discovery of the alkaloid, the attention of the investigators was focused mainly on its mydriatic properties. To Chen [1] belongs the honor of working out the complete pharmacology of ephedrine, which was found to be a sympathomimetic drug closely allied in its chemical constitution and physiologic action to epinephrine. Chemically, ephedrine differs from epinephrine in that it does not contain a phenolic hydroxyl group, but has an extra methyl radical which accounts for its more persistent effects and greater stability, permitting oral administration of the drug and sterilization of its solutions by boiling. The physiologic effects of ephedrine are similar to sympathetic stimulation and consist in a rise in blood pressure due to cardiac stimulation and vascoconstriction, inhibition of intestinal movement, relaxation of bronchial musculature and stimulation of the uterine musculature. When applied locally, ephedrine causes mydriasis without changes in accommodation, and rapid shrinkage of the nasal mucosa. Experiments on animals have proved it to be of low toxicity, and continued use has shown that injury to any organ or tolerance to the drug has not developed.

For details of the chemistry and pharmacology of ephedrine, the reader is referred to the original articles by Chen,[1] and by Chen and Schmidt.[2]

* From the Department of Medicine, University of California Medical School.

* Read before the Annual Meeting of the California State Medical Association in Los Angeles, April 25, 1927.

1. Chen, K. K.: A Pharmacognostic and Chemical Study of Ma Huang, J. Am. Pharm. A. **14**:189, 1924; The Effect of Ephedrine on Experimental Shock and Hemorrhage, Proc. Soc. Exper. Biol. & Med. **22**:203, 1924; The Effect of Repeated Administration of Ephedrine, ibid. **22**:568, 1925; The Acute Toxicity of Ephedrine, ibid. **22**:404, 1925; A Comparative Study of Ephedrine, Tyramine and Epinephrine, J. Pharmacol. & Exper. Therap. **28**:59, 1926.

2. Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine: The Active Principle of the Chinese Drug Ma Huang, J. Pharmacol. & Exper. Therap. **24**: 339, 1924; The Action and Clinical Use of Ephedrine, J. A. M. A. **87**:836 (Sept. 11) 1926.

The ephedrine, in the form of its crystalline hydrochloride, used in our study was obtained from Dr. B. E. Read at the Peking Union Medical College by Dr. W. J. Kerr, and at his instigation tried out at the University of California allergy clinic and in certain cases in the wards of the University Hospital. Its clinical effects were studied in the following conditions: chronic vascular hypotension, shock, bronchial asthma, hay-fever, toxic erythema, urticaria and angioneurotic edema.

HYPOTENSION

Chronic Vascular Hypotension.—The use of ephedrine in hypotension naturally suggested itself as soon as it was learned from animal

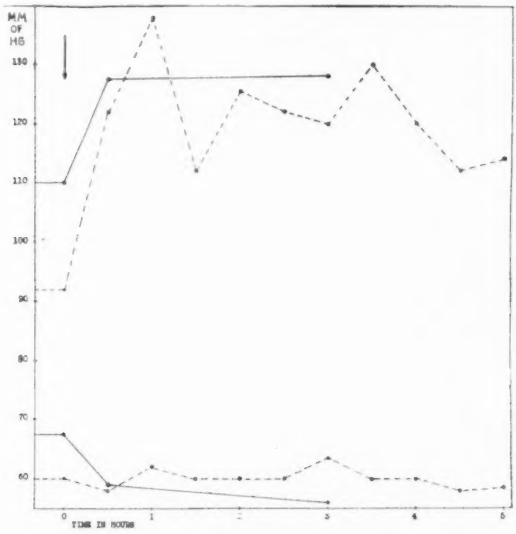

Chart 1.—Curves showing blood pressure of patient number 39 (weight 147 pounds) after the administration of 25 and 50 mg. of ephedrine by mouth. The solid line indicates the blood pressure after the administration of 25 mg. of ephedrine; the broken line, after 50 mg. The arrow indicates when ephedrine was given.

experiments that this drug is capable of producing a sustained rise in blood pressure extending over a period of at least several hours.

Ephedrine was given to nine patients who had chronic vascular hypotension with a consistent systolic blood pressure of between 93 and 108. Eight of these patients were men, and one was a woman. All but three were hospital cases. In most cases the drug was given in doses of 50 mg., three times a day, by mouth. In all cases a rise in the systolic pressure amounting to between 9 and 46 mm. was observed in from

five minutes to an hour, and the blood pressure remained above the initial level for four hours or more. The diastolic pressure was inconstant, but showed some rise in most cases. The variations of the diastolic pressure were between — 10 mm. and + 10 mm. Charts 1 and 2 represent blood pressure curves in three patients with hypotension following the administration of ephedrine.

For comparison with the blood pressure curves of patients with vascular hypotension, the effects of ephedrine on normal blood pressures

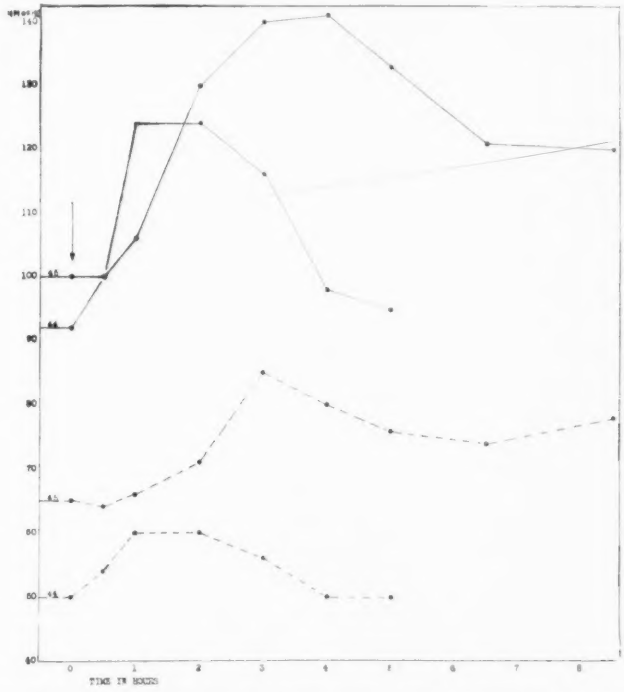

Chart 2.—Curves showing blood pressure of patient number 44 (weight 124 pounds) and 45 (weight 143 pounds) after the administration of 100 mg. of ephedrine by mouth. The solid line indicates the systolic blood pressure; the broken line, the diastolic. The arrow indicates when ephedrine was given.

were studied. The results as recorded in chart 3 show that these do not differ in any way from those in average cases of hypotension. It would appear that the amount of increase in the systolic blood pressure from ephedrine is independent of the weight of the patient, as suggested by the fact that a dose of 50 mg. of ephedrine has increased the blood pressure by 9 and 44 mm. in two patients weighing 95 pounds (43.1 Kg.)

and 148 pounds (67.1 Kg.), respectively, but that the same dose will produce the same increase in blood pressure on different days in the same person, and that the action of the drug is, within certain limits, roughly quantitative for the same patient. This can be seen from the fact that in case 39, the administration of 25 mg. of ephedrine increased the systolic blood pressure by 18 mm., while 50 mg. of ephedrine increased it by 46 mm., and in case 43 the increase after the administration of 50 mg. was 10 mm., while after 75 mg. it was 17 and 18 mm. on two different days (charts 2 and 3). In cases 44 and 45, 50 mg. of ephedrine raised the systolic blood pressure 14 and 15 mm., and 100 mg. of the drug increased it 32 and 41 mm., respectively.

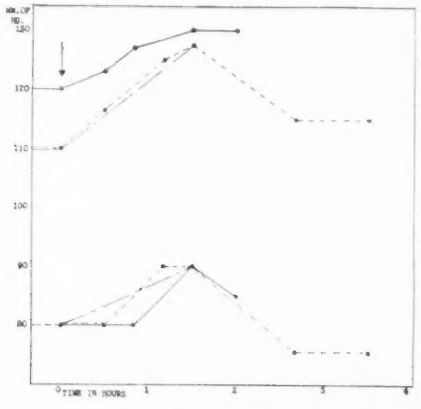

Chart 3.—Curves showing blood pressure of patient number 43 (weight 179 pounds) on successive days after the administration of 50, 75 and 75 mg. of ephedrine by mouth. The solid line indicates the blood pressure after the administration of 50 mg. of ephedrine; the regularly broken line, after 75 mg., and the irregularly broken line, after 75 mg. of ephedrine. The arrow indicates when ephedrine was given.

In seven patients with chronic hypotension to whom ephedrine was given regularly for from eight to thirty-seven days with an average of twenty days, the blood pressure was raised at all times of the day during the period of administration of ephedrine. The smallest increase in the average blood pressure was 4 mm. systolic and 2 mm. diastolic, and the greatest was 24 mm. systolic and 9 mm. diastolic with an average of 14.3 systolic and 5.3 diastolic for all cases. Details of the individual cases will be found in table 1. In none of these cases were there any objective signs of improvement besides elevation in blood pressure. As far as the subjective symptoms were concerned, three of the patients felt stronger, while four did not notice any change.

In the way of undesired effects, one patient had insomnia and another had marked palpitation for several hours after the administration of a single dose of ephedrine.

On the whole, from our limited experience in the treatment of patients with chronic vascular hypotension with ephedrine, the conclusion can be drawn that the blood pressure level can be raised in these cases, and that about half of the patients feel subjectively stronger while taking the drug. Miller,[3] and Rowntree and Brown[4] have

TABLE 1.—*Blood Pressure of Patients with Hypotension During Ephedrine Therapy*

Case	Dose of Ephedrine	Time of Observation During Administration of Ephedrine in Days	Average Blood Pressure: Before Administration of Ephedrine, Systolic	Before Administration of Ephedrine, Diastolic	After Administration of Ephedrine, Systolic	After Administration of Ephedrine, Diastolic	Average Increase in Blood Pressure, Systolic	Average Increase in Blood Pressure, Diastolic	Symptomatic Effects
39	25 mg. in a. m.	19	99	60	114	68	15	8	Patient felt stronger and warmer while on ephedrine
40	50 mg. three times a day	21	98	60	113	68	15	8	Patient was stronger, and felt warmth in feet which were usually cold; some insomnia
41	50 mg. three times a day	22	96	70	107	67	11	−3	Patient felt better in general
42	50 mg. three times a day	16	95	53	112	56	17	3	None
5*	50 mg. four times a day	37	96	60	110	70	14	10	None
20*	50 mg. three times a day	8	108	60	132	69	24	9	None
26*	50 mg. three times a day	21	108	65	112	67	4	2	None

* Patient also had asthma.

reported a maximum rise of from 10 to 50 mm. in the systolic blood pressure and similar symptomatic results with ephedrine therapy in their cases of hypotension.

Acute Hypotension of Shock.—Chen[5] was the first to try ephedrine in experimentally produced shock and hemorrhage in animals. As a result of these experiments, he indicated in an early article the possibility

3. Miller, T. G.: Ephedrine: Its Use in the Treatment of Vascular Hypotension and Bronchial Asthma, Ann. Clin. Med. **4**:713, 1926.

4. Rowntree, L. G., and Brown, G. E.: Ephedrine Therapy in Addison's Disease, Endocrinology **10**:301, 1926.

5. Chen (footnote 1, second reference).

of using it in similar conditions in man, and pointed out that theoretically ephedrine therapy can be successful only if hemorrhage is not excessive and when the patient is seen early. He also mentions the possibility of using the drug as a prophylactic agent before protracted operations.

We had the opportunity to use ephedrine in such conditions twice. In the first case, in which shock followed a postoperative hemorrhage in a man 80 years of age in whom the blood pressure had dropped from 185 systolic and 95 diastolic to 70 systolic and 30 diastolic, the patient was treated with 100 mg. of ephedrine, three times a day, by mouth. The patient improved rapidly, and his blood pressure was up to its previous level two days after the administration of ephedrine was started. However, it is impossible to draw definite conclusions from this case, since with ephedrine the patient received a transfusion of blood and was given caffeine.

In the second case, one of surgical shock in a man, aged 58, in whom the blood pressure decreased from 110 systolic and 78 diastolic to 65 systolic and 0 diastolic, the patient was treated with ephedrine after transfusion of blood and medication with caffeine had failed to improve his condition. He received four doses of 100 mg. of ephedrine at hourly intervals. An hour after the first dose, a reading of the blood pressure could not be obtained. An hour after the second and third doses the blood pressure was from 60 to 70 systolic and 0 diastolic. An hour after the fourth dose, the blood pressure was again unobtainable, and a little later the patient died. In this case ephedrine medication, used as a last resort, was probably begun too late to be of any benefit. In the literature, Miller [5] and Chen and Schmidt [6] reported several cases of surgical shock in which the patients were treated with ephedrine. In most of these cases, ephedrine therapy did not give beneficial results even when the drug was given intravenously. In a later paper, Chen and Schmidt [7] expressed the opinion that ephedrine may be injurious to the heart, which is impaired in shock through a deficient coronary circulation. Rudolf and Graham [8] have reported good results from ephedrine medication in early cases of acute hypotension following spinal anesthesia, and as a prophylactic before such anesthesia. The evidence accumulated to date concerning the value of ephedrine therapy in acute hypotension of shock forces one to conclude that its beneficial effect is doubtful, and that favorable results can be expected only if it is given early or as a prophylactic.

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6. Chen and Schmidt (footnote 2, first reference).

7. Chen and Schmidt (footnote 2, second reference).

8. Rudolf, R. D., and Graham, J. D.: Notes on Sulphate of Ephedrine, Am. J. M. Sc. **173**:399, 1927.

ASTHMA AND HAY-FEVER

On the strength of Chen's [6] demonstration of the capacity of ephedrine to produce relaxation of the bronchial musculature in experimental animals in which artificial spasms of the bronchi were induced by physostigmine, Miller [9] gave the drug orally to several asthmatic patients in 1925 and obtained good results. Following the publication of this work, treatment with ephedrine was started in a series of patients at the University of California allergy clinic, including thirty patients with bronchial asthma, three patients with hay-fever and nine patients with both bronchial asthma and hay-fever, a total of forty-two cases. Our group of patients with hay-fever is small, owing to the fact that the present work with ephedrine was done between the months of August and March when practically all cases of hay-fever caused by pollen are quiescent. Only patients in the active stage of the two conditions were selected for ephedrine medication, and no other form of treatment was used in conjunction with this drug.

Clinical data concerning the individual cases which were deemed essential in the evaluation of the therapeutic results of ephedrine in each case, namely, the age of the patient, duration of the condition, frequency and severity of attacks, allergic status and previous treatment are summarized in table 2, together with the dose and method of administration of ephedrine, the symptomatic effects and the undesirable effects.

Asthma.—In asthma, in addition to the foregoing data, determinations of the vital capacity were repeatedly made on nineteen patients, both before and after ephedrine therapy. The best vital capacity between attacks as compared to the theoretical normal vital capacity calculated for each patient according to Dreyer's work, "The Assessment of Physical Fitness," served to indicate the amount of permanent functional impairment of the lungs caused by asthma, and thus furnished an objective criterion concerning the severity of this condition in our patients as a group. The average vital capacity of our group was 81 per cent of the calculated normal. Patients with cardiac diseases were not included in this group. A still more useful application of measurements of vital capacity was found in objectively judging the severity of individual paroxysms of asthma and the degree of bronchial relaxation afforded by ephedrine and epinephrine. Finally, measurements of vital capacity were used as a check on the patient's statement in regard to symptomatic relief after the administration of ephedrine in an attack.

Ephedrine was given in doses of from 25 to 100 mg. The frequency of administration varied from one dose, as needed for paroxysms of asthma, to doses given four times a day. As a rule, the patients were

9. Miller, T. G.: A Consideration of the Clinical Value of Ephedrine, Am. J. M. Sc. **170**:157, 1925.

TABLE 2.—*Clinical Data of Patients with Asthma and Hay-Fever*

Case	Age	Clinical Diagnosis	Duration of Condition in Years	Frequency of Attacks	Severity of Attacks	Protein Sensitization	Previous Treatment	Ephedrine: Dose	Ephedrine: Method of Administration	Symptomatic Effects	Undesirable Effects
1	64	Asthma	8	Mild attacks daily; severe attacks from 3 to 4 times a week	+++	Negative	Epinephrine	25 to 50 mg. as circumstances required	Oral	Complete relief	None
2	40	Asthma	3	Every few months for several days	++	Negative	Epinephrine	25 to 50 mg. as circumstances required	Oral	Complete relief	None
3	54	Asthma	38	All year, from 4 to 5 attacks a day	+++	Positive	Potassium iodide; Shipman's powders	25 mg. twice a day	Oral	Complete relief	Some nervousness, mild diuresis and constipation
4	27	Asthma	22	Weekly	+ to +++	Negative	Epinephrine calcium chloride i. v.; inhalations of stramonium; bact. vaccine	50 mg. three times a day	Oral	Partial relief	None
								25 to 50 mg. as circumstances required	Hypo.	Complete relief	
5	28	Asthma	27	Daily in winter	++	Negative	Epinephrine "Asthmador"	50 mg. four times a day	Oral	Partial relief	None
6	21	Asthma	19	Daily	++ to +++	Negative	Epinephrine; bact. vaccine; calcium chloride i. v.; sodium iodide	50 mg. four times a day	Oral	Complete relief	None
7	53	Asthma and hay-fever	2	Daily	++	Positive	Sodium iodide	50 mg. three times a day	Oral	Complete relief	None
								3 per cent	Nasal spray		
8	29	Asthma	6	Daily	++ to +++	Negative	Epinephrine; asthma cigarettes; bact. vaccine; potassium iodide	50 mg. three times a day	Oral	Partial relief	Nausea
9	26	Hay-fever	4	Daily	++	Positive	Bact. vaccine	50 mg. three times a day	Oral	Partial relief	Nervousness, palpitation, insomnia
								3 per cent	Nasal spray		None
10	36	Asthma	7	Daily	+++	Negative	Epinephrine; potassium iodide	25 mg. one dose	Oral	No relief	Marked palpitation all night
11	50	Asthma and hay-fever	18 5	Daily	+++	Negative	Epinephrine; potassium iodide; belladonna cocaine	25 mg. four times a day	Oral	No relief	Insomnia, nervousness, palpitation, nausea, vomiting
12	45	Asthma	6	Nightly	++	Negative	Epinephrine; belladonna; potassium iodide	25 to 50 mg. at night	Oral	Complete relief	None

13	61	Asthma	15	Continuous	++	.....	Epinephrine; potassium iodide	25 mg. four times a day	Oral	Complete relief	Slight nausea at times
14	23	Asthma and hay-fever	7	Nightly	++	Negative	Potassium iodide	25 to 50 mg. four times a day	Oral	Partial relief	Marked nervousness and insomnia
15	43	Asthma and hay-fever	All life	Several times a year; last attack 4 months continuous	+++	Negative	Epinephrine	50 mg. three times a day	Oral	Complete relief	None
16	52	Asthma	12	Nightly	++	Negative	Epinephrine; bact. vaccine; belladonna; potassium iodide	50 mg. three times a day	Oral	Partial relief	None
17	23	Asthma	11	Daily from 4 to 5 times	+++	Negative	Epinephrine four times a day; potassium iodide	50 to 100 mg. three times a day	Oral	Partial relief, (epinephrine only once a day)	None
18	34	Asthma	3	Daily	++	Negative	Epinephrine; potassium iodide	50 mg. three times a day	Oral	No relief	None
19	28	Hay-fever	3	Daily	+	.....	None	25 mg. in a. m.	Oral	Complete relief	None
20	66	Asthma	10	Nightly	++	.....	?	50 mg. three times a day	Oral	Complete relief	None
21	25	Asthma and hay-fever	1	Daily	++	Negative	?	50 mg. three times a day	Oral	Partial relief	None
22	47	Asthma	10	Daily in winter	++	.....	.....	50 mg. as circumstances required	Oral	Complete relief	Some tremor
23	39	Asthma and hay-fever	23	Irregularly every few months	+ to +++	.....	Bact. vaccine	50 mg. as circumstances required	Oral	Complete relief	None
24	54	Asthma	All life	Seasonal with cold weather	+ to +++	.....	Epinephrine	50 mg. three times a day	Oral	Partial relief	None
25	56	Asthma	15	Continuous	+++	Negative	Belladonna; potassium iodide	50 mg. three times a day	Oral	Partial relief	None
26	51	Asthma	12	Every few weeks	++	Positive	Epinephrine	50 mg. three times a day	Oral	Complete relief	None
27	23	Asthma	21	From 1 to 2 times a month for from 1 to 3 days	++	Negative	Ephinephrine	50 mg. as circumstances required	Oral	Complete relief	None
28	24	Asthma and hay-fever	14	Continuous, worse in winter	+ to +++	Negative	.....	25 to 50 mg. at night	Oral	Complete relief	None
29	19	Asthma	15	Nightly	+++	.....	Epinephrine	50 mg. three times a day	Oral	Complete relief	None

TABLE 2.—*Clinical Data of Patients with Asthma and Hay-Fever—Continued*

Case	Age	Clinical Diagnosis	Duration of Condition in Years	Frequency of Attacks	Severity of Attacks	Protein Sensitization	Previous Treatment	Ephedrine: Dose	Ephedrine: Method of Administration	Symptomatic Effects	Undesirable Effects
30	40	Asthma	1½	Continuous	+	.....	Atropine; codeine	25 to 50 mg. three times a day	Oral	Partial relief	None
31	46	Asthma and hay-fever	32	Beginning at age of 14, for 2 years; 30, for 1 year; now for 3 months	+ to +++	Positive	Epinephrine	100 mg. three times a day	Oral	Marked relief in attacks; no attacks if taken regularly	None
32	52	Asthma	6	Weekly to daily.....	+++	Negative	Epinephrine; potassium iodide; morphine	50 mg. as circumstances required	Oral	Complete relief	None
33	31	Asthma	8	Monthly for 1 week.....	++	Negative	"Rhinex"; "asthma serum"	25 mg. three times a day	Oral	Partial relief	Some nervousness
34	22	Asthma	21	Every 2 to 3 months; now constant	++	.....	Epinephrine	50 mg. three times a day	Oral	Partial relief	None
35	78	Asthma	40	Beginning at age of 33, for 9 months; now daily for 2 years	+++	.....	Epinephrine; potassium iodide	50 mg. as circumstances required	Oral	Complete relief	None
36	30	Asthma	20	Daily	++	Negative	Epinephrine; potassium iodide	25 to 50 mg. as circumstances required	Oral	Complete relief	Insomnia
37	34	Asthma	1½	Two to three days weekly	+	Positive	.....	25 mg. as circumstances required	Oral	Complete relief	None
38	30	Asthma	10	One week every month..	+	.....	.....	25 mg. as circumstances required	Oral	Partial relief	
		Hay-fever		All year round.....	.....	.....	.....	3 per cent	Nasal spray	Complete relief	Fulness in head
46	59	Asthma	13	Nightly	++	Positive	Vaccine; sodium iodide; Tucker's remedy	50 mg. at night	Oral	Partial relief	Insomnia all night
47	37	Asthma	1	One year ago, nightly for 2 months; now for 3 months nightly	+++	Positive	Epinephrine; belladonna; cigarets	50 mg. at night and as circumstances required	Oral	Complete relief	None
48	19	Asthma	13	Every 2 days to 2 weeks, lasting 1 hour to 4 days	+++	Positive	"Asthmadore"; belladonna; epinephrine	50 to 100 mg. as circumstances required	Oral	Marked relief	None
49	16	Hay-fever	13	All year round.....	++	Positive	.....	3 per cent	Nasal spray	Marked relief	None

accorded great freedom in adjusting the dose and frequency of administration. In all but three patients, the drug was given orally. In three cases, ephedrine was given hypodermically during attacks of asthma for purposes of comparison, and in only one case was this method adopted as a routine procedure for severe attacks. This was done because the patient was getting only partial relief when the drug was taken orally, while he obtained complete relief with subcutaneous administration; at the same time, the unpleasant effects of epinephrine were obviated.

The therapeutic effects of ephedrine were classified in the table under the headings of "complete relief," "marked to partial relief" and "no relief" on a subjective-symptomatic basis, since our experience dealt with clinic patients in whom only occasional paroxysms of asthma were observed by one of us. We feel satisfied that the reports of "complete relief" by the patients are reliable, because over three fourths of our patients who gave this response had had previous injections of epinephrine for asthma and therefore presumably knew what "complete relief" meant. The other two headings are self-explanatory. Of thirty-nine patients with bronchial asthma, twenty-one (or 54 per cent) obtained complete relief from their paroxysms when ephedrine was taken after the onset of the paroxysm, and continued administration of the drug usually greatly reduced the number of attacks or prevented them altogether. Marked to partial relief was obtained by fifteen (or 38 per cent) of our patients. When ephedrine was taken regularly in this group, it often prevented the paroxysms, although after onset an attack could not be controlled completely by it. Three patients did not obtain benefit from ephedrine medication.

On careful analysis of the clinical data in our series of cases of asthma, it was found that the age and sex of the patients, the duration of the condition, the frequency and severity of the attacks, the coexistence of hay-fever and the allergic status did not play an important rôle in the degree of success with ephedrine therapy.

The only factor that had some influence in this sense was the previous treatment received by the patient for asthma, as most of the marked untoward symptoms necessitating the withdrawal of ephedrine in spite of the relief of asthmatic symptoms by the drug occurred in patients in whom the administration of epinephrine had been stopped immediately preceding ephedrine medication.

In table 3 we have compiled the results of ephedrine therapy in cases of asthma and hay-fever as reported in the English and foreign literature to date, making a total of over 330 cases. A comparison of results given by various writers shows that the percentage of successes, partial successes and failures is much the same in all series.

In our experience, symptomatic relief from oral administration of ephedrine was obtained in from five to thirty minutes. The following

TABLE 3.—*Our Results with Ephedrine Therapy in Bronchial Asthma and Hay-Fever with a Summary of Results in the Literature to Date*

	Asthma				Hay-Fever				Undesirable Effects		
	No. of Cases	Complete Relief	Partial Relief	No Relief	No. of Cases	Complete Relief	Partial Relief	No Relief	None	Slight	Marked
Present report	39	21	15	3	12	7	4	1	29	7	6
Miller (Am. J. M. Sc. **170**: 157, 1925)	7	4	2	1	..	..	..	..	..	Occasionally	Never
Miller (Ann. Clin. Med. **4**: 713, 1926)	36	26	4	6	..	..	..	..	..	Occasionally	Never
Middleton and Chen (Arch. Int. Med. **39**: 385 [March] 1927)	25	9	8	8	..	..	..	..		Not mentioned	
Kammerer and Dorrer (München. med. Wchnschr. **73**: 1739, 1926)	8	4	3	1	..	..	..	..	4	3	1
Pollak and Rabitschek (Wien. klin. Wchnschr. **39**: 753, 1926)	16	14	2	0	..	..	..	..	"Some"	"Some"	1
Jansen (Klin. Wchnschr. **5**: 2402, 1926)	Not given	"Same results as Pollak and Rabitschek"									
Hess (München. med. Wchnschr. **73**: 1691, 1926)	15	"Some"	"Some"	"Rare cases"	..	..	..	..		Not mentioned	
Thomas (Am. J. M. Sc. **171**: 719, 1926)	20	Relief 17		3	..	..	..	..	..	..	Occasionally
Wearn (J. A. M. A. **87**: 836 [Sept. 11] 1926)	6	6		0	..	..	..	..		Not mentioned	
Rudolf and Graham (Am. J. M. Sc. **173**: 399, 1927)	2	1		1	..	..	..	..		Not mentioned	
McDermot (Canad. M. A. J. **16**: 422, 1926)	20	"In most cases"		..	..	..	..	..	..	Some patients	2
Balyeat (J. Oklahoma M. A. **20**: 3 [Jan.] 1927)	"More than 100"	"Of considerable value in at least 65%"		20%	Not given	Relief sometimes for a few minutes		20%	..	..	20%
Gaarde (Am. J. M. Sc. **172**: 588, 1926)	..	..		..	26	"Good Results" 13	"Fair Results" 5	8	..	Most patients	

case (no. 2) may serve as an illustration: The patient came to the clinic during an attack of asthma, with the vital capacity reduced from the usual 53 per cent of normal to 20 per cent and a blood pressure of 115 systolic and 90 diastolic. Fifty milligrams of ephedrine were given by mouth. Five minutes later, the patient had obtained complete symptomatic relief; her vital capacity was increased to 30 per cent of normal (or by 50 per cent), and her blood pressure was 130 systolic and 95 diastolic. Fifteen minutes after taking the drug, her vital capacity was 33 per cent of normal, and her blood pressure was 135 systolic and 95 diastolic. Such prompt action of ephedrine given orally, which has already been reported by McDermot, would almost make one look for a psychic explanation if it were not for the fact that complete symptomatic relief was accompanied by marked increase in the vital capacity and a considerable elevation in the blood pressure, which indicates that the action of the drug was responsible for all of these changes (charts 4 and 5).

Hypodermic administration of ephedrine during acute attacks of asthma in two of our patients took full effect in one and one-half and ten minutes, respectively). The first of these patients (no. 27) obtained complete symptomatic relief one and one-half minutes following a hypodermic administration of 50 mg. of ephedrine, while the blood pressure increased from 118 systolic and 78 diastolic to 130 systolic and 78 diastolic in five minutes and remained at this level. The second patient (no. 31), who on previous occasions obtained marked but not complete relief from oral administration of ephedrine, was seen during an attack of asthma when the vital capacity was reduced from 89 per cent of normal to 32 per cent, and the blood pressure was 125 systolic and 97 diastolic. He was given 100 mg. of ephedrine hypodermically in view of his weight (184 pounds), and ten minutes later had obtained his maximum but not complete relief from the drug. The vital capacity at that time had increased to 40 per cent of normal (or an increase of 25 per cent), and the blood pressure had risen to 130 systolic and 98 diastolic. Fifteen minutes after the first dose the patient received another injection of 100 mg. of ephedrine, which in ten minutes raised the blood pressure to 136 systolic and 97 diastolic, but failed to give complete symptomatic relief or to increase the vital capacity. The condition of this patient remained the same for over an hour, when an injection of $\frac{1}{150}$ grains (0.0004 Gm.) of atropine completely relieved the residual symptoms (charts 4 and 5).

At another time the same patient was seen in a more severe attack of asthma, which reduced his vital capacity to 12 per cent of normal, the blood pressure being 132 systolic and 100 diastolic. This time an injection of 0.5 cc. of 1:1,000 solution of epinephrine was given to compare

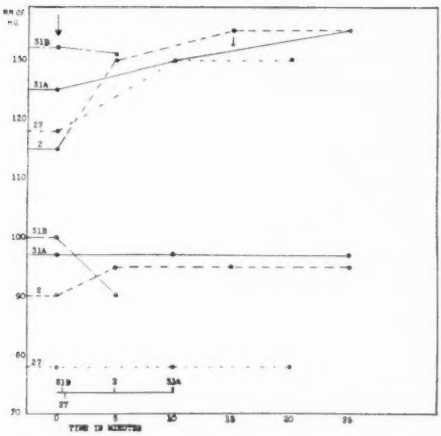

Chart 4.—Curves showing blood pressure of three asthmatic patients after the administration of ephedrine and epinephrine during an attack. Number 2 indicates the curve for patient number 2 (weight 120 pounds) after the administration of 50 mg. of ephedrine by mouth; number 27 indicates the curve for patient number 27 (weight 166 pounds) after 50 mg. of ephedrine hypodermically; number 31A indicates the curve for patient number 31 (weight 184 pounds) after 100 mg. of ephedrine hypodermically repeated after fifteen minutes, and number 31B indicates the curve for the same patient after the administration of 0.5 cc. of epinephrine hypodermically during another attack. The lowest curve indicates the time of disappearance of symptoms for each patient. The arrow indicates when ephedrine was given.

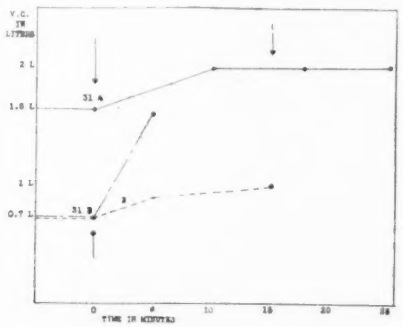

Chart 5.—Curves showing vital capacity of two asthmatic patients after administration of ephedrine and epinephrine during attacks. Number 2 indicates the vital capacity for patient number 2 (between attacks 1.6 liters) during an attack and after the administration of 50 mg. of ephedrine by mouth; number 31 A indicates the vital capacity for patient number 31 (between attacks 4.4 liters) during an attack after the administration of 100 mg. of ephedrine hypodermically repeated after fifteen minutes, and number 31B indicates the vital capacity of the same patient in another attack and after the administration of 0.5 cc. of epinephrine hypodermically.

its action with that of ephedrine. After the injection of epinephrine, the patient obtained complete symptomatic relief in about one minute with an increase in the vital capacity to 40 per cent of normal (or by 333 per cent) and a blood pressure of 130 systolic and 90 diastolic five minutes after the injection was given (charts 4 and 5).

These two cases serve well to illustrate that the action of ephedrine given by injection is generally more prompt than when the drug is given orally, but that it is slower than the action of epinephrine. The last case is also a good demonstration of the fact that epinephrine will give complete symptomatic relief when ephedrine fails to do so. This case also verifies the impression of all who have used ephedrine in the treatment of patients with asthma that it brings about a greater amount of bronchial relaxation, though the exact extent of this cannot be ascertained until patients with asthmatic attacks of the same severity, as shown by the decrease in vital capacity, have been treated with both drugs on different occasions.

Several writers who have had experience with ephedrine therapy recommend combining ephedrine with epinephrine for patients with asthma who are not relieved by ephedrine alone. In the few cases in which we have tried such a combination, severe nausea and vomiting occurred. Only one patient benefited temporarily by the combination of these two drugs, as ephedrine medication by mouth reduced the number of daily injections of epinephrine from four to one; but eventually he developed nausea and vomiting and had to discontinue the practice. As further evidence of an apparent incompatibility of ephedrine and epinephrine can be cited the fact already mentioned that most of our patients in whom marked undesirable effects of ephedrine supervened were receiving epinephrine up to the time when they were started on ephedrine. In this connection it is interesting to recall that Chen [10] has shown by animal experiments that ephedrine and epinephrine have a synergistic action. Therefore, the possibility must be considered that marked untoward symptoms in these cases were due to synergism of the two drugs; in other words, that these patients were really getting an overdose. A rather dramatic incident pointing in that direction occurred to one of our patients to whom 0.8 cc. of a 1:1,000 solution of epinephrine was given for an attack of asthma which was partially relieved by 100 mg. of ephedrine taken twelve hours before the injection of epinephrine. Immediately after the injection, the patient complained of a severe suboccipital pain, the onset of which was simultaneous with a complete disappearance of asthmatic symptoms. The blood pressure, which was 150 systolic and 104 diastolic just before the injection, rose in one minute to 240 systolic and 110 diastolic, and it took two inhala-

10. Chen (footnote 1, fifth reference).

tions of amyl nitrite and two doses of $\frac{1}{100}$ grains (0.00065 Gm.) of nitroglycerin to bring it down to its previous level after a period of forty minutes. A decision on this question can be arrived at after it is seen whether smaller doses of ephedrine and epinephrine given in conjunction will produce sufficient bronchial relaxation to relieve an asthmatic attack without causing excessive undesirable effects.

While ephedrine markedly increases the vital capacity during an acute attack of asthma, it does not seem to bring about permanent improvement of the functional capacity of the lungs, as a comparison of readings of the vital capacity between attacks before and after ephedrine therapy indicates. We obtained an average increase of 0.2 liters in all patients with asthma who were given ephedrine in whom such readings were taken, which, of course, is negligible in view of the considerable fluctuations of the readings of the vital capacity from day to day in asthmatic subjects. This observation is not astonishing if it is remembered that the permanent reduction of vital capacity in asthmatic subjects is produced by emphysema for which the asthma is responsible but not by the asthma per se.

The only type of asthma in which ephedrine theoretically would be able to effect an increase of the vital capacity between acute attacks is one in which the patient is having a mild spasm of the bronchioles all of the time, with exacerbations of this spasm in the form of acute attacks. An illustration of such a case is furnished by the patient in case 3, and the results obtained with ephedrine therapy over a period of six months are given in chart 6. When the patient came to the clinic, attacks of asthma were continuous day and night, with from four to five severe attacks every twenty-four hours. She was given a dose of from 25 to 50 mg. of ephedrine three times a day and as circumstances required. The drug completely controlled the individual attacks of asthma but unfortunately caused a number of undesirable symptoms, namely, nervousness, palpitation, constipation, diuresis and marked insomnia if taken at night. After experimenting for several days, it was found that the patient obtained the greatest comfort with the least amount of undesirable symptoms when given 25 mg. of ephedrine twice a day (after breakfast and after lunch); she has been on this dosage for the last six months. Knowing that we were interested in the results of ephedrine therapy, the patient expressed her gratitude to us by keeping a daily record of her attacks, which we have reproduced in chart 6. The chart shows not only abrupt diminution of the number of attacks a week after ephedrine therapy was started, but also a more gradual diminution of the frequency of attacks during the six months while the patient was being treated with ephedrine. Three months after the beginning of the administration of ephedrine, when determinations of vital capacity were started, the vital capacity was 54 per cent of normal. The patient's lung capacity

gradually increased under treatment, until two months later it had reached 100 per cent; it has remained at practically the same level. Such marked improvement cannot be explained on the basis of season variations, since it occurred during the months of November and December, when California has its rainy season.

We feel that a few words should be said in regard to the blood pressure in asthmatic patients who are receiving ephedrine, because our observations in this regard differ materially from those of other workers who have made statements to the effect that the blood pressure is little affected in these cases. Chen [7] explains this lack of rise in the blood pressure by differences in the pulmonary circulation.

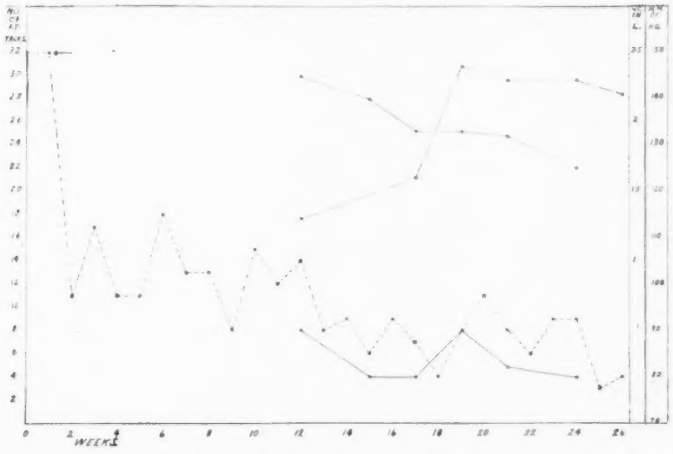

Chart 6.—Chart showing blood pressure, vital capacity and number of weekly attacks of asthma in patient number 3 (weight 98 pounds) who was given 25 mg. of ephedrine by mouth twice daily for six months. The regularly broken line indicates the number of attacks a week; the irregularly broken line, the vital capacity, and the unbroken line, the systolic and diastolic blood pressure. The arrow indicates when the administration of ephedrine was started.

On the contrary, it has been our experience to observe rises in blood pressure in asthmatic patients that in no way differed in degree, time of onset or duration from those in patients free from asthma. This applies to blood pressure curves obtained after single doses of ephedrine, as can be seen in the three curves in chart 4, and also to the more constant increase in the blood pressure level produced by the regular administration of ephedrine. As can be learned by glancing at table 1, the average increase in blood pressure in three patients with asthma, who also had hypotension, was 14 mm. systolic and 7 mm. diastolic as against an

average increase of 14.5 mm. systolic and 4 mm. diastolic in four patients with hypotension who were free from asthma.

A notable exception to this rule, which we found to be true in all cases in which systematic estimations of the blood pressure were carried out, is presented in case 3; in the course of the last four months on ephedrine therapy, the blood pressure of this patient decreased from 146 systolic and 90 diastolic to 135 systolic and 80 diastolic (chart 6). We feel that more observations over a longer period of time on this and other patients are required before a definite opinion can be formulated; but the possibility of a parallel between this case, in which prolonged administration of ephedrine was carried out, and cases in which marked hypotension bordering on Addison's disease developed after long continued medication with epinephrine, must be kept in mind.

Hay-Fever.—The dosage and frequency of administration of ephedrine for hay-fever was the same as for asthma. With one exception, the drug was given at first by mouth; in two cases, oral administration was later supplemented by a 3 per cent nasal spray in order to obtain complete relief; in one case, oral administration was replaced by the spray to obviate marked untoward symptoms. One patient was given ephedrine only by the nasal spray. In none of these cases was the nasal mucosa irritated as so often happens after the administration of epinephrine. The results of ephedrine therapy were classified under the same headings as those of asthma. Of twelve cases of hay-fever, complete relief was obtained in seven (or 58 per cent); marked to partial relief was given by the drug in four cases (or 33 per cent), and complete failure occurred in one instance.

As can be seen from table 3, our experience with ephedrine in hay-fever is in fairly close agreement with that of Gaarde,[11] and differs from that reported by Balyeat,[12] who sometimes obtained only transient relief from symptoms in his cases of hay-fever.

Untoward Effects.—Disagreeable effects from ephedrine medication in the form of nausea, nervousness, insomnia, palpitation and, rarely, constipation and diuresis were met with in 30 per cent of our cases, and in 12 per cent these were so severe that the administration of the drug had to be discontinued. The undesirable effects met with in the treatment of patients with asthma and hay-fever are classified in table 3 according to the degree of severity, as are also the disagreeable symptoms reported in the literature whenever any statements regarding them were made. As pointed out before, the most severe untoward symptoms that

11. Gaarde, F. W., and Maytum, C. K.: The Treatment of Hay-Fever with Ephedrine, Am. J. M. Sc. **172**:588, 1926.

12. Balyeat, R. M.: Use of Ephedrine in Asthma and Hay-Fever, J. Oklahoma M. A. **20**:3 (Jan.) 1927.

we noted occurred in patients who received epinephrine up to the day when they were given ephedrine. It is possible that by combining sedatives with ephedrine medication many of the undesirable effects of this drug can be eliminated or at least considerably lessened.

To investigate the effects of the repeated administration of ephedrine, Chen [13] gave this drug in daily doses for a month to a number of rabbits and white rats, and reported no pathologic changes at autopsy in any organs in these animals. With a view of determining whether any possible renal changes take place in man, we began to analyze the urine before and after ephedrine medication. Although we have not done this in a sufficient number of cases and have not followed our cases in this respect long enough, it may be well to mention in a preliminary way that in a group of fifteen patients, several showed red blood cells or casts in the urine after being given ephedrine therapy for a short time. These observations show that the question of renal irritation from ephedrine seems to be one worthy of investigation. In this connection, a recent article by Starr [14] deserves mention. He discusses the production of transient albuminuria caused by renal vasoconstriction after the administration of ephedrine, and makes a statement to the effect that he obtained evidence showing that ephedrine is not intrinsically injurious to the kidney; unfortunately, the nature of this evidence is not given. Rudolf and Graham [8] also do not report signs of renal irritation in ten of their cases.

Tolerance.—The question of tolerance to ephedrine is interesting because of the great similary of this drug to epinephrine, repeated administrations of which result in a certain tolerance. Evidence obtained by Chen [13] from experiments on animals tends to show that tolerance does not develop after repeated administrations of ephedrine for a month. On the other hand, in five patients in our series of cases of asthma and hay-fever, or in fully 15 per cent of the patients to whom ephedrine was given over any length of time, the beneficial effects of ephedrine have suffered considerable diminution in the course of time, and in four patients in whom complete relief was obtained at first, only partial relief was reported later, while in one patient in whom partial relief was afforded at first, the drug ceased to give any relief after a short time. In addition, two of our patients showed acquired tolerance to ephedrine by reporting the disappearance of the nausea which at first accompanied the taking of the drug. In reporting his series of asthma

13. Chen (footnote 1, third reference).

14. Starr, I., Jr.: The Production of Albuminuria by Renal Vasoconstriction in Animals and in Man, J. Exper. Med. **43**:31, 1926.

cases in which the patients were treated with ephedrine, Balyeat [12] also comments on the fact that in some cases the continued use of the drug causes unpleasant effects to disappear. The same experience is related by Kammerer [15] in his paper.

OTHER CONDITIONS

Toxic Erythema.—Spectacular results were obtained in a case of extensive toxic erythema accompanied by pruritus, as five minutes after the patient had taken 65 mg. of ephedrine by mouth, the erythema disappeared, and the itching ceased. The erythema recurred on the next day over a limited area, but again promptly disappeared after the same dosage of ephedrine.

Urticaria.—Ephedrine was given to seven patients with urticaria. In five of these cases, no improvement was noted either in the appearance of the rash or in the intensity of subjective symptoms. In two patients, definite improvement was observed, but the time which elapsed between the beginning of ephedrine therapy and the relief from urticaria was compatible with spontaneous recovery.

Two of the patients who failed to improve after the administration of ephedrine were given one injection of epinephrine each, and in one of them considerable improvement was noted shortly after the injection.

Miller [9] is the only author who has used ephedrine in urticaria and reported his results in two cases; in one subjective relief and in the other disappearance of the rash were observed following administration of this drug.

Angioneurotic Edema.—Three patients with angioneurotic edema failed to react favorably to the administration of ephedrine. One of these patients improved markedly after two injections of epinephrine. Following the injections, this patient was treated with ephedrine, and the edema did not recur.

SUMMARY

Hypotension.—Chronic Hypotension: Ephedrine, usually in doses of 50 mg., three times a day, was given to a number of patients who had hypotension; this was followed by a maximum increase in the systolic blood pressure of between 9 and 46 mm. and a sustained average elevation in the systolic blood pressure of 14.3 mm. We observed the same increase in the systolic blood pressure in patients with normal blood pressure and in those affected by asthma. The diastolic pressure varied between — 10 mm. and + 10 mm., with some rise in most cases. It appears that the amount of rise in the systolic blood pressure is inde-

15. Kammerer, H., and Dorrer, R.: Kunze Mitteilung über die Wirkung des Ephedrine-Merck auf Asthmakranke, München med. Wchnschr. **73**:1739, 1926.

pendent of the weight of the patient, but is constant in the same patient and within certain limits roughly proportionate to the dose of ephedrine.

Repeated administrations of ephedrine, besides increasing the blood pressure level in these patients, imparted to some of them a feeling of strength and well-being.

Acute Hypotension: Ephedrine was given to two patients in a state of surgical shock. In one case the patient recovered, but, since at the same time transfusion of blood and caffeine medication were given, it is hard to tell how much was accomplished by ephedrine. The other patient died.

Asthma and Hay-Fever.—Thirty-nine patients with asthma and twelve patients with hay-fever were treated with ephedrine, which served to control the attacks and, when used constantly, to prevent them in many instances. Ephedrine therapy gave complete relief in 56 per cent and partial relief in an additional 24 per cent of our cases. In 8 per cent of the cases, failures were due to absence of relief, and in 12 per cent of the cases to marked untoward symptoms.

Oral administration gave relief in our cases in from five to thirty minutes, and hypodermic administration acted more promptly. Compared to epinephrine, ephedrine acted more slowly and less completely; the action, however, continued much longer, and in most cases the disagreeable by-effects of epinephrine were avoided. Combination of these two drugs in our experience often produced marked untoward symptoms.

Undesirable effects from ephedrine medication in the form of nausea, vomiting, nervousness, insomnia and palpitation were encountered in 30 per cent of our cases, and in 12 per cent of the cases these symptoms were so severe that the administration of the drug had to be discontinued. Some degree of tolerance to ephedrine was obtained in at least 15 per cent of our patients.

Other Conditions.—In one case of toxic erythema, spectacular recovery was obtained with ephedrine. In seven cases of urticaria, the benefit from ephedrine therapy was doubtful in two and absent in five. Three patients with angioneurotic edema failed to improve after the administration of ephedrine.

CONCLUSIONS

1. Ephedrine may be of benefit in some cases of chronic hypotension.

2. The results of ephedrine therapy in acute hypotension of shock are doubtful.

3. In asthma and hay-fever, ephedrine is of great value, completely controlling attacks in about half of the cases and giving partial relief in another one fourth of the cases.

4. The advantage of ephedrine over epinephrine are that it is effective when given by mouth, that its action is longer, that it does not pro-

duce local irritation when given as a nasal spray, and that in most cases undesirable symptoms, such as tremor and palpitation, do not occur as with epinephrine.

5. Among the disadvantages of ephedrine are: (*a*) failure at times to relieve asthmatic attacks when epinephrine is effective and (*b*) in occasional cases, untoward symptoms which are more marked than those following the administration of epinephrine.

6. The use of ephedrine in urticaria and angioneurotic edema is not promising.

MYCOTIC GASTRITIS *

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Since the thrush organism is found in the mouths of a large proportion of normal persons (Merke,[1] 35 per cent, Brünstein,[2] 40 per cent), and gastric conditions are particularly favorable for the growth of the various molds (Askanazy[3]), it is not surprising to learn that the normal stomach quite frequently harbors fungi. Although Kirch and Stahnke[4] were unable to demonstrate the presence of molds in the aspirated contents of the stomach in any of thirty cases, the positive observations obtained by others (Moppert and Kagen,[5] Cafasso[6] and Hartwich[7]) are sufficiently conclusive to indicate that the occurrence of fungi in the intact stomach, if not universal, is at least widespread. The observation of molds in twenty of thirty-two normal stomachs viewed by Crasset[8] at postmortem examinations in cases in which contamination from the pharynx and esophagus was eliminated lends further support to this view. On the basis of available evidence, it can be safely assumed that when fungi are present in the intact stomach, they play little if any rôle in the production of gastric disease. In fact, the frequency with which these organisms are found in stomachs of normal persons has led to the assumption that they represent harmless saprophytes. The symptoms attributed in the older literature, especially before the advent of the roentgen ray, to molds which were found in the aspirated contents

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1. Merke, F.: Ueber die Bedeutung des Soorpilzes für das chronische Magengeschwür, Beitr. z. klin. Chir. **130**:549, 1924.

2. Brünstein, A.: L'oidium albicans dans la bouche des personnes saines, Thèse, Gènève, 1907.

3. Askanazy, M.: Ueber Bau und Entstehung des chronischen Magengeschwürs sowie Soörpilzbefunde in ihm, Virchows Arch. f. path. Anat. **250**:370, 1924.

4. Kirch, E., and Stahnke, E.: Pathologisch-anatomische, klinische, und tierexperimentelle Untersuchungen über die Bedeutung des Soorpilzes für das chronische Magengeschwür, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:174, 1923.

5. Moppert, G. G., and Kagen, G.: Recherches sur la presence de muguet (oidium) dans le liquide gastrique d'individus normaux et d'individus atteints d'ulcere et de cancer de l'estomac, Rev. méd. de la Suisse Rom. **42**:505, 1922.

6. Cafasso, K.: Ueber das Vorkommen des Soorpilzes im Magensafte beim Ulkus und bei anderen Erkrankungen des Magens, Med. Klin. **18**:828, 1922.

7. Hartwich, A.: Ueber das Vorkommen von Soor im chronischen Magengeschwür, in hämorrhagischen Erosionen und Magencarcinomen, Virchows Arch. f. path. Anat. **241**:116, 1923.

8. Crasset, referred to by Askanazy (footnote 3, p. 456).

of the stomach in all probability were due to undiscovered independent gastric lesions.

Although it is generally agreed that the presence of fungi per se in the intact stomach does not lead to ill effects, opinions concerning the rôle of these parasites when associated with a gastric lesion vary widely. The presence of fungi in the walls of the chronic round ulcer of the stomach, an observation made by Heller [9] in 1895, received little attention until the appearance of Askanazy's [10] work in 1921. Askanazy was able to demonstrate the presence of fungi in more than one half of his series of cases of ulcer, and he ascribed to these organisms a rôle in the maintenance of the chronicity of the lesions. Notwithstanding the fact that some investigators have failed to demonstrate the presence of molds culturally or histologically in a large proportion of the chronic ulcers they have examined, Askanazy's work has received sufficient confirmation to justify the assumption that chronic ulcers quite frequently harbor mycotic organisms. Whether a relationship of cause and effect exists between the failure of an ulcer to heal and the fungi found in its base or walls is still a matter of controversy.

On the basis of extensive and well controlled investigation, Askanazy was led to assume in his first work [10] that the fungus did not represent an unimportant saprophyte when found in connection with an ulcer, the state of which would be identical whether the fungus was present or not. In a subsequent report,[3] this author gives the following reasons for believing that the mycotic organisms are of pathologic significance: their exceedingly frequent occurrence in freshly resected ulcers; the frequent correspondence in location of the fungi and the inflammatory reaction; the often intracellular location of the parasites; repeated invasion of the granulation tissue zone by the mycelia; apparent extension of the filaments into the blood vessels and even through the entire thickness of the gastric wall. Support is lent Askanazy by the observations and opinions of von Meyenburg,[11] Cafasso,[6] Hartwich,[7] de Vecchi [12] and Merke.[1] On the other hand, Nissen,[13] Aschoff,[14]

9. Heller, A.: Beitrag zur Lehre vom Soor, Deutsches Arch. f. klin. Med. **55**:116, 1895.

10. Askanazy, M.: Ueber Bau und Entstehung des chronischen Magengeschwürs sowie Soorpilzbefunde in ihm, Virchows Arch. f. path. Anat. **234**:111, 1921.

11. Von Meyenburg, H.: Ueber Schimmelpilzerkrankungen der Magenwand, Frankfurt. Ztschr. f. Path. **23**:86, 1920.

12. De Vecchi, referred to by Askanazy (footnote 3, p. 462).

13. Nissen: Ueber die Bedeutung des Soörpilzes fur das chronische Magengeschwür, Verhandl. d. deutsch. path. Gesellsch. **18**:283, 1921.

14. Aschoff, L.: Aussprache zu Nissen, Verhandl. d. deutsch. path. Gesellsch. **18**:287, 1921.

Sternberg,[15] Frank,[16] and Kirch and Stahnke [4] in their respective considerations of the subject attached little if any significance to the presence of fungi in the genesis or maintenance of the chronicity of peptic ulcer. The arguments pro and con were well summarized by Hauser,[17] who arrived at the conclusion that the presence of a fungous growth on the floor or margins of an ulcer may have some tendency to inhibit its healing. One should, he stated, assume, however, that this inhibitory effect is of minor importance as compared to the influence of other factors.

In addition to the group of patients with normal stomachs, in which the rôle of the fungus is admittedly an insignificant one, and the group with a simple ulcer, in which the importance of the mold is questionable, there is a third group in which characteristic pathologic lesions are produced, due directly to the effect of the fungi present. The last group includes patients with true mycotic gastritis, of which little or no mention is made in American or English literature. Einhorn,[18] Knapp [19] and Kellogg [20] dealt with the subject of fungi in aspirated gastric contents, but they did not refer to actual mycotic infection of the stomach. Careful search of the literature has failed to disclose any reports of mycosis of the stomach occurring in this country or in England. Therefore, a rather detailed report of the following case of mycotic gastritis appears warranted.

REPORT OF CASE

History.—H. R., a white man, aged 27, a chauffeur, on March 26, 1926, was admitted to the Women's and Children's Hospital in Chicago in the service of Dr. P. M. Stetler, who kindly furnished the following clinical account:

On admission the patient complained of persistent vomiting, weakness and occasional oozing of blood from the mouth and nose. He stated that three weeks prior to entrance, he had had an attack of grip which lasted two weeks and which was accompanied by infrequent nose bleeds. A week prior to entrance, he returned to work, and, on the following day, he was suddenly seized by severe epistaxis while driving his taxicab. He was taken to the Cook County Hospital, where a posterior nasal packing was introduced and horse serum administered. The following day, March 22, he returned home, and since that time he had been able to retain little food or water on account of vomiting. Blood was not seen in the emesis, nor was abdominal pain present at any time. In addition to

15. Sternberg, C.: Aussprache zu Nissen, Verhandl. d. deutsch. path. Gesellsch. **18**:286, 1921.

16. Frank, P. S.: Ueber die Beziehungen des Soörpilzes zu dem runden Magengeschwür, Wien. Arch. f. inn. Med. **5**:39, 1922.

17. Hauser, G.: Infektiöse und infektiös-toxische Einflüsse in Henke, F., und Lubarsch, O.: Handbuch der speziellen Pathologische Anatomie und Histologie, Berlin, 1926, vol. 4, p. 736.

18. Einhorn, M.: The Occurrence of Moulds in the Stomach and its Probable Significance, M. Rec. **57**:1025, 1900.

19. Knapp, M. I.: Gastrosia Fungosa, Am. Med. **10**:56, 1903.

20. Kellogg, J. H.: Moulds in the Stomach, M. News **77**:88, 1900.

the vomiting, since March 22 he had suffered from slight but daily oozing of blood from the inside of the left cheek and occasionally from nose bleeds.

With the exception of the resection of a rib undertaken for empyema five years previously and an accident seven months before admission, noteworthy information was not obtained from the past history. The accident which occurred July 17, 1925, was apparently severe; the patient was thrown against the steering wheel of his taxicab with such force that the wheel was broken. He suffered particularly from injuries to the arms and legs, on account of which he was unable to work for approximately four months. Following eating during this period, he had occasional attacks of vomiting which usually occurred in the forenoon. The attacks lasted only a few hours after which the patient was able to eat with little discomfort. In the family history, it was noted that the patient's mother had died of cancer of the stomach at the age of 35, and that two sisters had succumbed to tuberculosis.

Physical and Laboratory Examinations.—Physical examination disclosed a young man about 30 years of age, thin, but not emaciated, who appeared to be quite ill. The temperature, pulse and respiratory rates were normal. The essential changes consisted of a small ulceration on the anterior portion of the left side of the nasal septum covered with a gray exudate and a similar area on the inside of the left cheek opposite the last lower molar. There was physical evidence of a thickened pleura over the base of the left lung at the site of an old rib resection. The heart was slightly enlarged, and the second aortic tone accentuated. The blood pressure measured 140 mm. systolic and 90 mm. diastolic.

The urine had a specific gravity of 1.029 and contained albumin (++) and a few red cells, but no casts. The hemoglobin determination was 40 per cent, the red cell count 2,600,000 and the white cell count 10,600, 86 per cent of which were polymorphonuclears.

Subsequent Course and Treatment.—On the morning of entrance, the patient vomited undigested food but no blood. Nothing was given by mouth for forty-eight hours, fluids being supplied by hypodermoclysis and proctoclysis. Efforts to control the hemorrhage from the mouth and nose by chemical and actual cauterization proved futile, and a posterior nasal packing was required. The vomiting ceased for twenty-four hours, during which time the patient appeared to be improved. On the second day after entrance, a gastric lavage yielded an old blood clot (swallowed?) but no recent hemorrhage. The following day, the patient vomited clotted blood and a small amount of bright red fluid. On March 30, four days after admission, 500 cc. of blood was introduced into the patient's veins, following which he rallied; accordingly, another transfusion was performed on April 5. The patient appeared to improve until April 10, sixteen days following admission; that day, he vomited bright red blood approximately every hour. The emesis continued for a period of twenty-four hours, and then practically ceased. The erythrocyte count dropped to 900,000, and on April 12 a third transfusion was undertaken. Improvement in the blood picture occurred rapidly, the hemoglobin rising from 10 per cent to 45 per cent (recorded the day before death), following a fourth transfusion, while the red blood count increased to 2,000,000. On April 15, the temperature, which previously was below 100 F., had risen to 102 F. Later in the course of illness, physical symptoms of consolidation were elicited over the upper part of the right side of the chest, and a diagnosis of pneumonia was made. The patient became more and more toxic, and died on April 20, 1926.

Autopsy.—The postmortem examination was performed by Dr. R. H. Jaffe, whose anatomic diagnosis was: lobar pneumonia of the right upper and middle

lobes (gray hepatization); high grade chronic diffuse nephritis (secondary contracted kidneys); moderate anemia; localized mycotic gastritis; moderate hypertrophy of the left ventricular myocardium; edema of the lungs; hypostatic pulmonary hyperemia; petechial hemorrhages of the omentum; localized fibrous perihepatitis; fibrous pericholecystitis; slight bilateral hydronephrosis, and hemosiderosis of the liver.

Before passing to a detailed consideration of the stomach, it is important to know that the microscopic examination of the kidneys revealed a far advanced glomerulonephritis of sufficient degree to account for uremic manifestations and even death.

Fig. 1.—Mycotic gastritis. The flat membranous deposit encircling the cardio-esophageal juncture (*a*) extends distally over the surface of the stomach (*b*). A longitudinal section has been removed from the elevated, ragged excrescence (*c*).

Gross Description of the Stomach.—A well demarcated, greenish-gray membranous deposit (fig. 1 *a*) of rather irregular outline, averaging about 1 cm. in width, encircled the cardio-esophageal juncture. The prolongation (*b*) of this membrane passed distally over the region of the lesser curvature of the stomach for a distance of 3.5 cm. Most of the membrane was firmly attached to the underlying structure, especially on the gastric side, but in some areas it could be readily separated. The deposit was of uniform thickness and followed the folds of the

mucous membrane in its undulations. Contiguous with the membranous ring, there was found at the lesser curvature just beyond the cardia an elevated, olive-shaped, ragged mass (*c*) which measured 4 cm. in length and 1.5 cm. in its widest diameter; it was situated 1.3 cm. above the level of the gastric mucous membrane at its highest point. The center of the growth overlay the left gastric artery at the point of origin of several of its main branches. The long axis of this mass followed the line of the lesser curvature. The tissue which comprised this peculiar, shaggy prominence was a dirty greenish-gray and was soft, friable and irregular. The anterior and inferior margins of the growth were sloping, whereas the posterior and superior margins were slightly overhanging or straight. The surface of the growth, in general, was curved. In one place at the antero-inferior portion, an area approximately 0.5 cm. in diameter was discolored red

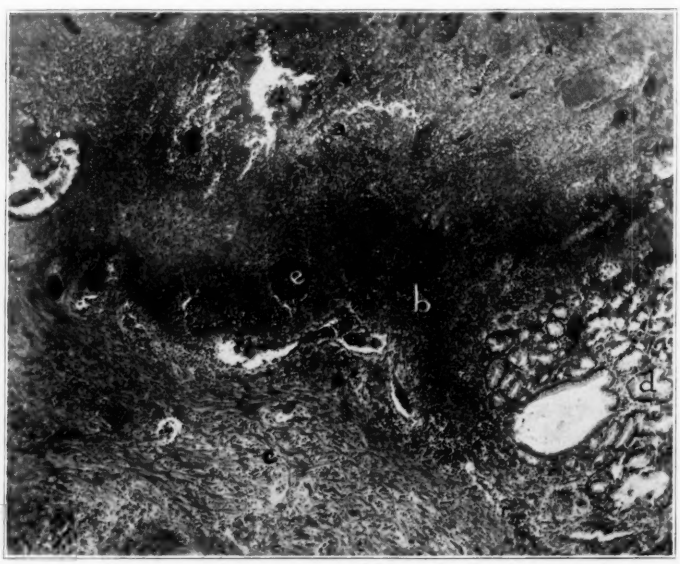

Fig. 2.—A section taken from the margin of lesion (*c*), figure 1. The necrotic layer (*a*) is delimited by a highly cellular zone (*b*) beyond which (*c*, *d*) the inflammatory reaction diminishes in intensity. One thrombosed vessel (*e*) can be readily identified.

by blood. When the growth was sectioned in its longitudinal axis, the greenish-gray mass was observed to have coalesced intimately with the mucous membrane, which had lost its architecture and could not be identified. The structureless tissue extended to the muscularis, which appeared to be intact. In a transverse section of the prominence, the well demarcated borders were more clearly seen; they were studded in many places with hemorrhagic extravasations and thrombosed blood vessels, which extended into the greenish-gray substance. At the anterior and inferior margins, where the mass sloped, the structureless, hemorrhagic tissue was seen to have insinuated itself between the mucosa and the subjacent layer, which raised the former but did not depress the latter. Evidence of previous ulceration,

either acute or chronic, could not be found at the site of the lesions mentioned. The stomach appeared to be unchanged except for the localized involvement described.

Microscopic Examination.—Using a lens of low magnification (fig. 2), one could distinguish three separate zones in sections taken from the involved areas of the stomach. The upper (superficial) one (*a*) consisted of a necrotic mass, which in the case of the largest lesion was heaped up far above the level of the bordering mucous membrane, and extended downward into the wall of the stomach to involve, in places, the entire thickness of the mucosa and part of the submucosa. In sections taken from the regions of the flat deposits, the necrosis was seen to be more superficial, rarely reaching to the muscularis mucosae. The second zone (*b*), which more or less sharply separated the previous one from the

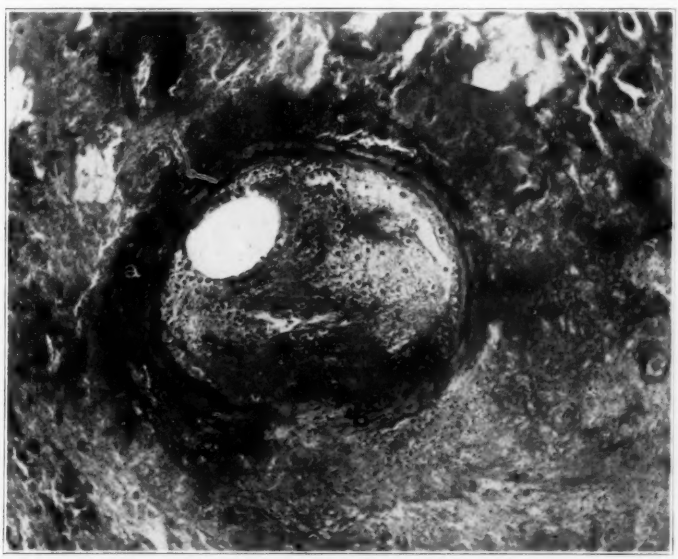

Fig. 3.—Photomicrograph of a thrombosed blood vessel located in the necrotic layer (fig. 2 *a*). In approximately three fourths of the circumference of the wall calcific deposits (*a*) are found, the remaining one-fourth (*b*) appearing relatively normal.

third, was represented by a dense band rich in cellular elements, with some hemorrhagic extravasations. The third zone (*c*) was occupied by relatively normal appearing tissue.

The necrotic zone, when viewed with a lens of higher magnification, was seen to be made up of structureless, pink material with many blue-staining foci, situated especially in the superficial layers and consisting of granular masses the morphology of which could not be identified in hematoxylin and eosin stained sections. The only elements in this area which retained their structure sufficiently to permit recognition were the blood vessels (fig. 2 *e*), the walls of some of which were fairly well preserved while others were represented by mere

shadows. Most remarkable, however, was the presence of calcific deposits in the walls of a number of blood vessels. In one such vessel (fig. 3), the deposition of lime (*a*) embraced approximately three fourths of the circumference of the vascular wall, while the remaining one-fourth (*b*) presented a relatively normal appearance. Recent hemorrhage is indicated by the presence of intact red blood cells found more particularly near the surface of the lesion.

The necrotic and the relatively normal zones were separated by an area of intense inflammatory reaction which for the most part demarcated the living from the dead tissue more or less sharply. This limiting membrane was composed of many round cells, together with a moderate number of polymorphonuclear leukocytes, macrophages and plasma cells. These cells were densely packed in some places, and separated by edema fluid and fibrin in other places. Proliferative changes were not prominent; there were a few spindle-shaped fibroblasts, and only slight multiplication of the endothelial cells had occurred. At the margins of the inflammatory zone, the glandular elements of the mucosa showed little evidence of growth. Within this demarcating wall, the vessels were dilated and distended with blood. Rupture of some of the blood channels had apparently occurred and was indicated by the presence of free red cells and blood pigment.

When one passed to the third zone, a more or less gradual transition to the normal was seen, and the reactive phenomena became less and less marked toward the serosa, so that this layer and the muscularis appeared to be practically unchanged. This description applies particularly to the main lesion (fig. 1 *c*). Sections taken from areas covered by the flat membranous deposit (fig. 1 *a* and *b*) showed essentially the same processes in varying degrees of extent and intensity. Histologic examination of the wall of the stomach at points remote from the grossly visible lesions disclosed a diffuse infiltration of the interglandular stroma of the mucosa by round and plasma cells in rather large numbers. Although thick walled vessels were frequently encountered in the mucosa of the grossly normal portions, calcification of the vascular walls was nowhere observed.

In sections stained by the Gram-Weigert method, the surface of the necrotic area appeared to be purplish-violet. In many places, the violet material extended irregularly into the deeper parts, gradually becoming less dense and finally fading out into the fine processes. The purplish-violet material, which for the most part was limited to the upper half of the necrotic layer, did not extend beyond the zone of inflammatory reaction. Under oil immersion magnification, it was found that the deep-staining masses on the surface were composed of spherical bodies of different sizes; all, however, were considerably larger than cocci. These globoid structures exhibited a distinct tendency to form irregular groups, the smallest of which were composed of from four to sixteen round elements. In the larger groups, the spheres were often so densely packed as to obscure their individual characteristics. Many fine, long threads were found lying between the round bodies in the deeper part of the purplish-blue material. These filaments (fig. 4), especially with a change of focus, showed distinct branching (*a*), which for the most part was angular. The free end of many of the threads showed bulbous thickenings. Many of the filamentous elements were made up of round granules arranged in linear formation (*b*). In the deeper parts of the necrotic layer, the spheroidal bodies were lacking, and only the filaments could be seen. These were found to invade a number of the small blood vessels, apparently having penetrated the adventitial and muscular coats. Well preserved threads were not noted in the lumen of the thrombosed vessels.

COMMENT

In the light of the postmortem observations, it appears reasonable to assume that the epistaxis and bleeding from the mouth were to be ascribed indirectly to the marked changes in the kidneys. To what extent nephritis was responsible for the gastric symptoms and what effect the mycotic gastritis had on the function of the stomach were somewhat conjectural. The old blood clot obtained by lavage performed the second day after admission to the hospital might well be attributed to the swallowed blood following the nasal packing. The emesis of blood clots and a small amount of bright red fluid recorded on the third day after entrance could likewise be explained (although with less prob-

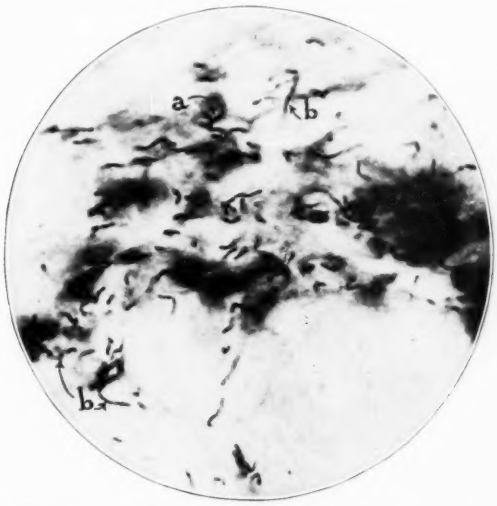

Fig. 4.—Threadlike organisms in the deeper portions of the necrotic area. One of the filaments shows distinct branching (*a*) while several are granular (*b*).

ability) on the same basis. It is likely, however, that the hematemesis which occurred hourly on April 10 was due to the effect of the fungous growth. It was this history of vomiting of blood, together with the appearance of the lesion, which led Dr. Jaffe to diagnose mycotic gastritis at the autopsy table. The fungus from the morphologic appearance seemingly belonged to the streptothrix (*Nocardia*) group, the spheroidal bodies representing spores (*Conidia*) and the branched threads, mycelia.

GROSS PATHOLOGIC LESIONS OF MYCOTIC GASTRITIS

In a survey of the literature on mycotic gastritis, one is struck by the divers and widely different lesions in the individual cases. In an attempt

at classification, the possibility suggested itself that these various lesions might represent different stages in the same process. If one reviews the separate reports with this thought in mind, it will be found that practically all of the pictures described can be satisfactorily explained on one pathogenic basis. The essential lesion is a focal inflammatory one, associated with vascular damage, which is apparently responsible for the accompanying necrosis. The development of the mycotic lesion finds a somewhat rough analogy in the genesis of the ulcer resulting from typhoid. The first stage in mycotic gastritis is characterized by formation of membrane due to the parasitic growth, followed by hemorrhagic necrosis of the underlying mucous membrane, production of slough and ulceration.

The membrane may develop in an intact stomach; in that event, however, general debility or a catarrhal inflammation of the gastric mucosa (Maresch [21]) is usually present; or the mycotic infection may be secondary to a gastric imperfection which favors the lodgment of molds on the defective site. In a case described by Klebs,[22] microscopic examination showed that the patient had an intact epithelium covered by a membrane consisting entirely of fungi. Such a case may be considered one of primary mycotic gastritis. Marchand [23] related that an 18 year old girl partook of a dish of decomposed mushrooms which, according to this author's interpretation, led to multiple hemorrhagic erosions, some of which were invaded secondarily by molds. It is difficult and at times impossible to distinguish between primary mycotic lesions associated with hemorrhage and hemorrhagic erosions on which a fungous growth has developed secondarily. The cases of gastric ulcer in which the presence of molds can be demonstrated, but in which little if any change is discernible in the gross appearance of the primary lesions, are not to be looked on as instances of mycotic gastritis.

The membrane which forms as a result of the fungous growth varies in color, frequently being green or gray and at times yellow or white. An admixture of brown or red, presumably due to imbibition of blood pigment, is commonly seen. The appearance of the membrane is similar to that observed in the pharynx and esophagus and, in fact, closely resembles a growth cultivated on an artificial medium. The deposits, which may be hemispherical, are, as a rule, elevated and flat, and often centrally depressed. These membranous deposits usually are

21. Maresch, R.: Zur Kenntniss der Soörmykose des Magens, Ztschr. f. Heilk. **28**:145, 1907.

22. Klebs, E.: Handbuch der pathologischen Anatomie, Berlin, 1869, vol. 2, pt. 1, p. 20.

23. Marchand: Ein eigentümlicher Magenbefund (Ulcus gangraenosum durch Fadenpilzwucherung) nach Vergiftung durch verdorbene Steinpilze, Verhandl. d. deutsch. path. Gesellsch. **14**:183, 1910.

sharply demarcated from the adjacent mucosa and not infrequently are surrounded individually by a narrow pale ring followed by a hyperemic hemorrhagic circular zone. The concentric arrangement of the rings gives the whole lesion the appearance of an iris.

The size of the individual lesion varies from that of a pinhead to a diffuse growth covering a broad surface or even the entire stomach. In von Wahl's [24] case, in which mycotic gastritis was first reported, the lesions were yellowish prominences the size of a pinhead and larger; they were isolated and coalescent and resembled the pustules of smallpox. In his case, Zalesky [25] described disseminated and confluent gray-white hemispherical and flat projections, varying in size from that of a pinhead to that of a lentil, and possessing central umbilication which likewise suggested a resemblance to the pustular eruption of variola. In Meyenburg's [11] third case, a group of tiny pustule-like prominences were found in the stomach of the patient. The lesions are as a rule larger than those described, in most of the cases varying in size from that of a lentil to several centimeters in diameter. Two involved areas are reported in Marchand's[23] case, one 2 by 3.5 cm., the other 4.5 by 6.5 cm., to be present in the patient. Buhl [26] related that in his case of gastric and intestinal mycosis there were sixty-two foci, varying in size from 2 mm. to 7 cm. in diameter. Occasionally a terrace-like arrangement formed by several colonies is encountered. In Löhlein's [27] first case, three such layers could be raised from each other. In Beneke's [28] report, the essential lesion consisted of a yellowish-green area made up of concentric deposits surrounding an ulcerated center. The lesions are practically always circular, except when they become confluent, in which event irregularity of outline results. A single extensive deposit is rarely found. In the case of the 18 months' old infant reported by Plaskuda,[29] the membrane involved not only the pharynx and esophagus, but extended beyond the cardia over almost the entire surface of the stomach to form a complete gray-brown lining of the gastric lumen. From the standpoint of height, a great variety in the lesions is noted. In Meyenburg's [11] three cases, the surface of the membrane extended just barely above that of the surrounding mucosa, measuring from 0.1 cm. to 0.15 cm. in height. As a

24. Von Wahl, E.: Ueber einen Fall von Mykose des Magens, Virchows Arch. f. path. Anat. **21**:579, 1861.

25. Zalesky, N.: Ein Fall von Soor im Magen, Virchows Arch. f. path. Anat. **31**:426, 1864.

26. Buhl, L.: Mycosis intestinalis, Ztsc'hr. f. Biol. **6**:129, 1870.

27. Löhlein, M.: Ueber Schimmelmykosen des Magens, Virchows Arch. f. path. Anat. **227**:86, 1919-1920.

28. Beneke, R.: Ein Fall von Schimmelpilzgeschwür in der Magenschleimhaut, Ztschr. f. Path. **7**:1, 1911.

29. Plaskuda: Hauterkrankungen bei kachektischen Kindern. 1. Fall von Purpura mit ausgebreiteter Soorbildung im Magen, Berl. Klin. **1**:501, 1864.

rule, the level of the growth appears to be from 0.2 to 0.5 cm. In my own case, the development is a most luxuriant one, as the level of the lesion extended 1.3 cm. above that of the mucosa. There is an extreme variation in the number of foci, as recorded in some of the foregoing statements.

Necrosis of the superficial layers of the gastric wall underlying the central portion of the lesion occurs relatively early, and is demonstrated best in a cross-section (gross as well as microscopic) of the involved focus. This change is indicated by a crater formation, which lends more height to the margins of the lesion. In Buhl's [26] patient, a prominence 2 cm. in diameter with central umbilication appeared as though it were the seat of a superficial ulcer; a second larger lesion presented a similar appearance. The author called attention to the possible deception, for in both instances there was central depression without the loss of tissue substance. Teutschlaender [30] spoke of a tendency toward rather than real ulceration in these cases, with central necrosis and crater formation. As a matter of fact, it is difficult, at times, to decide from the gross appearance alone whether the excavation is the result of central necrosis and depression or of actual separation and extrusion of dead tissue.

The necrotic zone being, as a rule, well demarcated, sloughing readily occurs. The ulcer which follows is usually a superficial one. In von Meyenburg's [11] first case, five umbilicated defects in the mucosa were found, two of which were originally covered by black sloughs that were loosened in manipulation even though the specimen was carefully handled. In addition to a single large lesion, 5 cm. in diameter, with a slightly sunken center, on the wall of the stomach, Maresch [21] described a circumscribed defect which, according to this author, apparently represented the site of a previously cast-off slough. There were also three foci of necrosis covered by delicate deposits only slightly adherent to the underlying tissue. Löhlein's [27] second case was that of a patient who presented nine flat, sharply bordered ulcers which for the most part had fairly smooth, pale yellow floors. Some of these ulcers were circular or somewhat oval; others were irregular, apparently dependent on the outline of the cast-off slough, which was not always round. In many cases, the floor of the ulcer was uneven and shaggy and discolored dark red or black by blood, as in the cases of von Recklinhausen,[31] Beneke [28] and others. Although the ulceration is usually superficial, the necrosis at times extends deep into the gastric wall. In Benelli's [32]

30. Teutschlaender, O.: Mucormykose des Magens, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **29**:127, 1917.

31. Von Recklinghausen, F.: Mutiple Nekrosen der Magenschleimhaut, (*a*) Mykose der Magenschleimhaut, Virchows Arch. f. path. Anat. **30**:366, 1864.

32. Benelli: Mykose der Magenschleimhaut, Beitr. z. Path. Anat. u. z. allg. Pathol. **54**:619, 1912.

case, the patent did not have a funnel-shaped perforation, but a diffuse peritonitis was found which this author attributed to invasion of the entire thickness of the stomach wall by fungus.

The gastritis is not focal in all cases. Von Meyenburg [33] related a case in which the patient had puerperal sepsis complicated by a phlegmon of the stomach. Microscopic examination of the gastric wall showed a widespread invasion of the involved parts with mycelia. The author assumed the rather diffuse phlegmonous gastritis to be on a mycotic basis and secondary to the uterine infection. Askanazy [10] described a case of acute diffuse oidiomycotic gastritis which occurred in a 68 year old person following the operative removal of a pyloric ulcer and a gastro-enterostomy undertaken four days before death. The gross specimen presented the appearance of a diffuse, hemorrhagic, gelatinous inflammation. In many instances the mycotic lesions are not limited to the stomach. In a case of mycotic gastritis reported by Maresch,[21] the process extended to the stomach from a carcinoma of the esophagus. In one of von Meyenburg's [33] cases, the patient had metastatic abscesses on a mycotic basis in the liver. In a number of reports, esophageal involvement in the absence of ulceration in this organ is noted, particularly in children (Nauwerck,[34] Plaskuda,[29] Zalesky [25]). In a unique case, that of Buhl,[26] in addition to the involvement of the stomach, duodenum and intestines a marked mesenteric and retroperitoneal lymphadenitis, a hemorrhagic periadenitis and a bloody peritoneal exudate were found.

MICROSCOPIC APPEARANCE IN THIS CONDITION

From what has been said regarding the variations in the gross appearance of mycotic lesions, the degree of microscopic dissimilarity in the various cases can be deduced. Here, however, owing to the relative ease in identification of the pathologic processes, the changes in the separate reports lend themselves readily to classification. Teutschlaender [30] summarized the microscopic changes found in his patient under the following heads: necrosis, cellular infiltration, tissue proliferation, hyperemia, hemorrhage, edema, exudation of fibrin and vascular thrombosis. These processes in differing degrees and combinations represent the alterations described by other authors. The various changes can be grouped under the title of hemorrhagic inflammation with thrombotic tendencies.

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33. von Meyenburg, H.: Ueber einen Fall von Fadenpilzgeschwüren der Magenschleimhaut mit metastatischen Abzessen in der Leber, Virchows Arch. f path. Anat. **229**:30, 1920.

34. Nauwerck, C.: Mykotisch-peptisches Magengeschwür, München. med. Wchnschr. **42**:877 u. 908, 1895.

The membrane, as a rule, consists of intertwining mycelial elements which are frequently branching, often associated with ovoid or globose bodies (conidia), together with desquamated epithelial cells, leukocytes and cellular debris. At times, the morphology of the fungus is sufficiently characteristic in the histologic preparations to permit identification, as in Löhlein's [27] case, in which aerial hyphae carrying the distinctive fructification bodies led to recognition of the mold as *Aspergillus fumigatus*. According to Castellani and Chalmers,[35] the fungi often lose their characteristics when growing parasitically in the tissues, and only mycelial threads and round and oval yeastlike bodies are seen. This statement is borne out by von Meyenburg's [11] observation of a case in which *Aspergillus fumigatus* was obtained in culture, but the microscopic sections showed only branching threads and globoid swellings devoid of fructification forms.

The epithelial surface underlying the membrane may be intact, but most often superficial necrosis is met with, even in the early cases. The zone of necrosis usually corresponds to the central portion of the overlying membranous deposit, and assumes the form of a blunt wedge with the apex directed outward toward the serosa. The extent of the necrosis varies, but it usually does not spread beyond the muscularis mucosae. The membrane due to the death of the parasites also participates in this necrosis. Within this zone of dead tissue, evidence of hemorrhage, in the form of blood pigment both free and engulfed, is a prominent feature frequently associated with the outlines or shadows of thrombosed vessels.

Bordering the necrotic zone is a leukocytic wall in which polymorphonuclear forms most frequently predominate. Some of these cells are laden with blood pigment and fatty detritus. Associated with this cellular infiltration are the usual changes of inflammation. Particularly marked at times are the proliferative changes involving not only the spindle shaped and endothelial cells of the submucosa, but also the epithelial elements of the mucosa. The distribution of the exudative and proliferative changes correspond roughly to the location of the invading molds. The depth to which the mycelia penetrate differs in each case, extension to the serosa, as in Ljubimowa's [36] report, being exceptional.

Most remarkable in the microscopic picture, however, is the tendency of the organisms to invade the blood vessels, presumably leading to extensive thrombosis and hemorrhage, which characterize mycoses of the stomach as of other organs. The vascular changes, in turn, account

35. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, New York, 1920, ed. 3.

36. Ljubimowa, W. J.: Ein Fall von Ulcus ventriculi verursacht durch Schimmelpilze, Virchows Arch. f. path. Anat. **214**:432, 1913.

for the necrosis *en masse* of the superficial layers, which, likewise, is a distinctive feature of the typical lesion. Löhlein [27] postulated a chemotactic attraction for fungi by the circulating blood to account for the invasion of the muscle layer of the arterial wall by these organisms. The theory of the entrance of molds into the blood stream from a primary site in the throat was invoked to explain the multiple abscesses of the brain containing grossly visible mycotic colonies in the case described by Zenker.[37] In the later years, Wagner,[38] and subsequently Vogel,[39] were able to substantiate Zenker's assumption by demonstrating the organisms in histologic preparations of the walls of blood vessels. It was not, however, until Heller [9] discovered the presence of fungi in one third of the twenty-five cases he studied that the frequency of invasion of vessels was emphasized. The foregoing reports are concerned exclusively with pharyngeal and esophageal involvement.

The first observation of vascular invasion of the stomach by molds is credited to Parrot,[40] who described this phenomenon in children. In practically all reports of mycotic gastritis, including and following Marchand's [23] report, the presence of fungi in the walls of the stomach was noted. Whereas thrombosis is the usual outcome in the esophageal vessels, the added danger of peptic erosion is incurred in the stomach. Fungi are held responsible for profuse hemorrhage in a case reported by Pick.[41] The patient was a woman, aged 44, who, following a septic abortion, developed hematemesis and melena. The lesion, according to Pick, consisted of a small chronic ulcer in the floor of which a suppurative process had developed, which in turn led to erosion of a subjacent vessel. The suppuration was produced purely as a result of mycotic organisms, the elements of which could be seen in histologic sections invading the arterial wall. Askanazy [10] cited three similar cases (cases 18, 19 and 20) of hemorrhage complicating an ulcer associated with the presence of fungi. In the stomach of a patient who died from gastric hemorrhage, Merke [1] found a penetrating ulcer with an eroded vessel. The author attributed the fatal hemorrhage to the destructive effect of the branched mycelia which were found in the arterial wall. In all the cases of severe fatal hemorrhage mentioned, the primary lesion appears to have been a chronic round ulcer in which the base became secondarily involved by mycotic infection.

37. Von Zenker, F. A.: Krankheiten des Oesophagus, in von Ziemssen: Handbuch der speziellen Pathologie und Therapie, 1874, vol. 7, p. 192.

38. Wagner, E.: Zur Kenntnis des Soors des Oesophagus, Jahrb. f. Kinderh. 1868.

39. Vogel, A., in von Ziemssen: Handbuch der speziellen Pathologie und Therapie, 1874, vol. 7, p. 64.

40. Parrot, referred to by Heller: Beitrag zur Lehre vom Soor, Deutsches Arch. f. klin. Med. **55**:116, 1895.

41. Pick, L.: Arterienarrosion durch Soorpilze mit-todlicher Blutung, ein Beitrag zur Kenntnis der Oidiomykosen, Berl. klin. Wchnschr. **57**:798, 1920.

BACTERIOLOGY OF MYCOTIC GASTRITIS

Owing to the fact that cases of mycotic gastritis are so seldom recognized before the histologic examination reveals the true nature of the disease, bacteriologic studies are, as a rule, omitted. In a few instances, however, cultures have been made from the fresh material, or smears or teased preparations have been examined. In the case of a man, aged 58, who died from carcinoma of the esophagus and mycotic gastritis, Maresch [21] was able to cultivate *Aspergillus fumigatus*. He injected a growth of this organism into rabbits and produced a generalized mycosis. In von Meyenburg's [11] first case, the same organism was isolated in pure culture (except for the presence of *Bacillus subtilis*). In the cases reported by Rudnew,[42] the lesions were invaded by an organism identified as *Penicillium glaucum*. In Kundrat's [43] case of universal favus, lesions harboring the characteristic molds were found in the esophagus, stomach and large bowel. In the cases of Marchand,[23] Beneke,[28] Ljubimowa [36] and Teutschlaender,[30] the fungi were identified by morphologic criteria as belonging to the mucor group. In histologic preparations of his first case, Löhlein [27] was able to demonstrate aerial hyphae bearing fructification forms indicating an infection with *Aspergillus fumigatus*. It is not to be inferred that in all cases of aspergillosis characteristic forms of the organism appear in the tissue, for in von Meyenburg's [11] case, as previously mentioned, although the organism was identified culturally, the characteristic forms were not present in the histologic sections which would permit recognition. Von Meyenburg stated that the higher fungi are found especially in acute lesions, and that the lower molds are more frequently encountered in chronic cases. In the case herein reported, the circumstances and conditions under which the autopsy was performed did not permit immediate culture. It appears from a morphologic study that the causal organism belongs to the streptothrix (*Nocardia*) group.

SYMPTOMATOLOGY

It is difficult to formulate a definite clinical picture of a mycosis of the stomach, since the disease is usually encountered as the terminal event of an independent condition. Which manifestations to attribute to the primary illness and which to the complicating disease, is in a great measure conjectural. Even in cases of primary mycotic gastritis the evaluation of symptoms is not an easy task, owing to the frequent occur-

42. Rudnew, referred to by Petterson, A.: Zur Frage der Bedeutung der Fadenpilze für die pathologischen Veränderung des Magens, Deutsche med. Wchnschr. **28**:703, 1902.

43. Kundrat, H., in Schmidts Jahrbücher: Ueber Gastro-Enteritis favosa **206**:253, 1885.

rence of secondary bacteriologic invasion. Clinical recognition of fungus infection of the stomach, as for instance by gastroscopic examination or at operation, which up to the present has not been recorded, would aid materially in identifying the symptoms due solely to the effect of the molds.

From a study of the reports in the literature, it may be stated that in the average case in which the mycotic process is limited to the stomach the infection does not produce constitutional disturbance. When, however, as it occasionally happens, the fungus involvement is extensive, the general manifestations may be profound. The symptoms are those of an acute infection, without distinctive characteristics. In Buhl's [26] case, the numerous lesions throughout the gastro-intestinal tract of the patient were held accountable, in the absence of other pathologic processes, for the vomiting, collapse and death of the patient. At times, the gastric mycosis leads indirectly to systemic effects by permitting secondary invaders to gain entrance into the previously healthy tissues. In one of von Meyenburg's [11] cases, the general toxemia suggested the clinical diagnosis of typhoid fever. At autopsy, a mycotic gastritis and multiple metastatic abscesses of the liver were found. As von Meyenburg was able to demonstrate bacteria and no fungi in the hepatic abscesses, he considered the gastric mycosis the portal of entry for the pyogenic organisms that reached the liver. A somewhat similar case, a mycotic gastritis complicated by a diffuse purulent peritonitis, was reported by Benelli.[32] Clinically, the patient presented gastro-intestinal symptoms, followed by evidence of peritonitis. At autopsy fungi were found in the gastric lesion, but not in the peritoneal exudate. The author considered the fungus infection of the stomach as the primary lesion through which the entrance of bacteria into the peritoneal cavity occurred. In those cases in which an independent infectious process is present, as for instance in pneumonia, which existed in my own patient, a consideration of all the facts is necessary before assignment of systemic symptoms to any single cause is made.

In regard to the local manifestations, difficulty is likewise encountered in attempting to segregate the symptoms produced by the mycotic from those resulting from a concomitant condition. Zalesky [25] reported the case of a bottle-fed infant who died with gastro-intestinal symptoms on the eighteenth day of its life. The writer ascribed the vomiting and diarrhea to the extensive mycotic involvement found at the autopsy, although if one reads the clinical history, the possibility of a primary nutritional disturbance to account for the symptoms readily suggests itself. In my own case of mycotic gastritis, the explanation of the hematemesis, in view of the associated high grade nephritis and the history of bleeding from the nose and mouth, is by no means unequivocal.

As Teutschlaender [39] pointed out, the vomiting, especially the vomiting of blood, is the only symptom that can be assigned to fungus infection of the stomach. The finding of molds in the aspirated gastric contents is in itself of little diagnostic importance, but when associated with repeated vomiting of small amounts of blood, it might lead to the suspicion that a mycotic gastritis was present. When the hematemesis is severe, the underlying lesion is more likely to be a peptic ulcer, in the floor and walls of which fungi may or may not be present.

SUMMARY

From what has been stated regarding the relative rarity of mycotic gastritis, its occurrence most frequently (in the light of present knowledge) as a terminal event or complication and the inability to detect its presence by ordinary diagnostic methods, it is to be concluded that the condition is of little clinical importance. One gains the impression, however, that a final decision regarding the rôle of fungi, in primary and secondary disease of the stomach, should be withheld until further data have been accumulated. It is striking that in so many cases the nature of the lesion is recognized only after careful study. In a case in which death followed resection of a duodenal ulcer, Lang [44] identified a leptothrix, apparently from the ulcer, as the cause of the pylephlebitis and cholangitis that contributed to the patient's death. Just how frequently the presence of fungi is overlooked in similar cases is difficult to estimate. The indications are that molds are responsible for many infections in which bacteria are incriminated. More frequent routine search for fungi as well as for bacteria would aid in determining the frequency and importance of mycotic organisms in gastric disease.

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44. Lang, F. J.: Durch Leptothrix-Infektion bedingte Leberinfarcierung in einem Falle von callösem Ulcus duodeni, Virchows Arch. f. path. Anat. **234**:367, 1921.

THE POSSIBLE INCREASE OF GUANIDINE IN THE BLOOD OF CERTAIN PERSONS WITH HYPERTENSION *

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In a recent communication [1] we described a method for the determination of guanidine bases in the blood, and noted that certain patients suffering from arterial hypertension showed higher values than did normal persons.

Since this publication, the work has been carried forward and a definite improvement in the method has been achieved. The method differs from that previously described in that the guanidine bases are absorbed by blood charcoal from a filtrate made slightly alkaline, and subsequently are released from the charcoal by means of acidified alcohol. The details of this method have been described elsewhere,[2] but a summary of it will be given before discussing the results obtained.

METHOD

(1) Nitroprusside reagent

Stock solution:

10 per cent sodium nitroprusside
10 per cent potassium ferricyanide
10 per cent sodium hydroxide

Mix:

1 volume 10 per cent sodium nitroprusside
1 volume 10 per cent potassium ferricyanide
1 volume 10 per cent sodium hydroxide

Add 3 volumes of water to 1 volume of the mixed reagent.

The reagent is ready for use when the color has changed to a pale yellow, which takes about twenty minutes. One cubic centimeter of the reagent is employed for every 5 cc. of the solution to be tested. This reagent will ordinarily keep for twelve hours, but if a turbidity develops after a few hours, a fresh solution should be made for use.

(2) Blood charcoal—Merck's—purified by acid.

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1. Major, Ralph H., and Weber, C. J.: The Probable Presence of Increased Amounts of Guanidine in the Blood of Patients with Arterial Hypertension, Bull. Johns Hopkins Hosp. **40**:85, 1927.

2. Weber, C. J.: The Determination of Guanidine Bases in the Blood, Proc. Soc. Exper. Biol. & Med. **24**:712, 1927.

(3) Acidified alcohol—95 per cent alcohol containing 2 cc. of normal hydrochloric acid per hundred cubic centimeters.

(4) Standard guanidine solution.

Stock:

Dissolve 0.1542 Gm. of guanidine carbonate solution in 100 cc. of 0.1 normal hydrochloric acid and add a few drops of chloroform as a preservative. This solution contains 1 mg. of guanidine per cubic centimeter.

Standard:

Ten cubic centimeters of the stock solution made up to 1,000 cc. with distilled water gives a solution containing 0.01 mg. of guanidine per cubic centimeter.

Procedure:

Twenty cubic centimeters of blood are precipitated with tungstic acid as in the regular Folin-Wu procedure. (The two-thirds normal sulphuric acid is added first and then followed by the tungstate which enables one to obtain 50 cc. of filtrate more quickly.) Eighty cubic centimeters of the filtrate is taken and 6 drops (0.4 to 0.5 cc.) of 10 per cent sodium hydroxide added, followed by 0.5 Gm. of blood charcoal. (This may be added by means of a spoon, which delivers the proper amount—a 4 inch horn spoon is suitable.) The charcoal is brought into suspension by shaking and after two to five minutes, the mixture is filtered through a 9 cm. folded filter, care being taken to avoid loss of charcoal. The flask is drained as completely as possible, but the charcoal is not washed. After the filter paper has drained for five minutes, the charcoal and filter paper is put back into the same flask from which filtration was made. Twenty-five cubic centimeters of the acidified alcohol is now added and the flask corked tightly and shaken vigorously to bring the charcoal into suspension. The shaking should be repeated several times during the two hour period so that the charcoal is left in contact with the alcohol. The charcoal may be left in contact with the alcohol over night, when the yield will be slightly greater.

The charcoal is filtered from the alcohol, and 20 cc. of the alcoholic filtrate is evaporated to dryness on a water bath. (Care must be taken not to produce charring. The safest plan is to keep the temperature of the water bath just below boiling and to assist the evaporation with an electric fan.)

The residue is taken up in 7 cc. of water. One cubic centimeter is set aside for the creatine determination and 1 cc. for the creatinine determination. One cubic centimeter of the nitroprusside reagent is then added to the remaining 5 cc. The solution is poured into a centrifuge tube and centrifuged for about two minutes, to throw down the slight flocculant precipitate which forms at this point. The supernatant liquid is decanted into a colorimeter cup and read against the appropriate standard which was prepared simultaneously with the unknown.

Standard tubes:

Four tubes containing 2 cc., 3 cc., 4 cc. and 6 cc. of the standard guanidine solution are each made up to 10 cc., and 2 cc. of the reagent is added. If necessary, an extra tube containing 10 cc. of the standard guanidine solution may be added.

Calculation:

Standard set at 20.

$$\frac{20}{\text{Reading of unknown}} \text{ by } \frac{\text{mg. in standard}}{2} \text{ by } 21.9 = \left\{ \begin{array}{l} \text{mg. of guanidine bases calculated as guanidine per hundred} \\ \text{cubic centimeters of blood} \end{array} \right.$$

Since creatine produces some color with this reagent, it is necessary to make a correction for it. When making the creatine estimations on final filtrate, a

correction of 0.12 must be applied. Thus, if the reading is 1 mg. of guanidine and the creatine content of the final filtrate is 2 mg. per hundred cubic centimeters, the figure $2 \times 0.12 = 0.24$ must be subtracted from 1 mg. The correct reading then would be 0.76 mg. of guanidine.

This procedure differs slightly from the method described by Weber,[2] since the creatine estimations for the correction are made on the final filtrate, instead of on the Folin-Wu filtrate.

Although creatinine may produce color with this reagent, the development of color is much slower than in the case of guanidine. If the reading is made within five minutes of mixing the solution, the color produced by 1 mg. of guanidine is as great as that produced by 400 mg. of creatinine. The amount of creatinine in normal blood does not interfere with the readings. Creatine, on the contrary, develops the color rapidly, and a correction must always be made for its presence, as stated. The color obtained after correction for creatine is not due to creatine, since it persists after conversion of creatine into creatinine by autoclaving in an acid solution. We have not, however, removed the creatine before making determination, since experiments have shown us that autoclaving also diminishes, to some extent, the color given to the blood filtrate to which a known quantity of guanidine has been added. Urea is not present in the final filtrate and does not cause interference.

We have tested the accuracy of this method by the addition of known amounts of guanidine to the blood and have found that the average recovery has been 85 per cent when amounts varying from 0.2 mg. to 1.0 mg. per hundred cubic centimeters were added. The recovery is as high as 75 to 85 per cent, when amounts as small as 0.2 to 0.3 mg. per hundred cubic centimeters were employed—a percentage of recovery higher than by the older method. Because of possible variations in the chemicals employed and particularly in the blood charcoal, a series of recoveries have been carried out with each new batch of chemicals before employing the method.

The results obtained in a series of thirty-five persons with normal blood pressures are given in table 1. The average guanidine reading obtained in these patients has been 0.11 mg. per hundred cubic centimeters. Variations have been from 0.02 to 0.19 mg. Nearly one half of these readings showed less than 0.1 mg. per hundred cubic centimeters. These values are somewhat lower than those given by the previous method, although it was stated at that time that the accurate estimation of amounts lower than 0.2 mg. per hundred cubic centimeters could not be made by the older method. The modification of the method gives clearer filtrates which are more easily read, and permits the estimation of smaller amounts.

A series of readings in patients with arterial hypertension, most of them being cases of "essential hypertension" is shown in table 2. The series also includes some cases of nephritis with nitrogen retention. The table shows that although some of the patients with "essential hypertension" show normal values, the majority of the patients with "essential hypertension" show some increase over the normal "guani-

TABLE 1.—*Guanidine Readings Obtained in a Series of Thirty-Five Persons with Normal Blood Pressure* *

No.	Age	Blood Pressure	Protein Nitrogen	Creatinine	Creatine	Uric Acid	Guanidine Reading	Guanidine Corrected	Remarks
1	40	120/70	35.3	1.3	3.0	2.8	.24	.06	
2	36	110/80	31.5	1.25	3.9	2.8	.25	.02	
3	35	110/80	26.1	1.15	3.6	2.36	.26	.04	
4	47	132/80	33.3	1.4	4.6	5.0	.5	.22	
5	29	128/82	30.8	1.25	3.2	3.4	.26	.06	
6	21	120/86	30.8	1.4	3.0	4.1	.25	.07	
7	39	120/86	32.4	1.3	3.0	3.7	.24	.06	
8	40	134/96	33.3	1.4	3.1	3.46	.24	.05	
9	59	120/70	28.6	1.36	2.8	3.64	.36	.19	
10	43	110/80	32.0	1.4	3.8	2.53	.36	.13	
11	26	120/80	34.7	1.4	4.7	2.66	.4	.12	
12	37	108/86	32.0	1.3	4.6	2.66	.32	.04	
13	60	104/76	34.8	1.25	3.6	2.85	.38	.16	
14	36	100/70	40.0	1.3	3.2	1.75	.38	.19	
15	54	154/84	30.8	1.3	3.7	2.16	.38	.16	
16	47	100/58	35.6	1.25	3.75	3.2	.39	.17	
17	18	100/54	36.3	1.2	3.8	2.4	.36	.14	
18	48	120/80	32.0	1.25	3.2	2.16	.38	.18	
19	46	122/84	26.6	1.3	3.8	3.12	.32	.12	
20	48	154/90	30.7	1.25	3.7	2.76	.35	.13	
21	40	150/90	27.6	1.25	4.2	2.85	.33	.08	
22	50	94/54	34.8	1.25	3.6	2.76	.36	.14	
23	50	122/86	40.0	1.4	3.6	2.96	.38	.16	
24	42	122/84	43.0	1.3	4.6	3.6	.43	.15	Thrombo-angitis obliterans
25	50	146/74	30.5	1.25	3.7	2.6	.31	.09	
26	23	90/60	24.5	1.1	4.1	3.3	.33	.08	
27	28	110/104	27.6	1.2	4.0	3.6	.31	.07	
28	27	103/62	21.5	1.3	4.3	2.0	.36	.11	
29	47	140/80	29.2	1.3	4.9	3.46	.38	.09	
30	30	125/95	41.5	1.5	4.0	4.3	.43	.19	Lipoid nephrosis cholesterol 500
31	68	150/80	35.0	1.4	4.1	4.1	.38	.13	
32	26	122/80	25.7	2.0	3.7	3.1	.32	.10	
33	40	135/90	34.5	1.2	3.8	2.4	.24	.02	
34	70	150/86	30.3	1.2	2.5	3.6	.24	.03	
35	40	160/100	36.0	1.3	4.6	2.7	.47	.11	

* Blood chemistry in milligrams per hundred cubic centimeters of blood.

dine" values, while the patients with nephritis and nitrogen retention show marked increases in "blood guanidine."

These observations suggest the importance of two pertinent inquiries. Are the slight increases in the group of "essential hypertension" of any significance? Can the increase in "blood guanidine" in chronic nephritis be due to an error of the method in oxidizing the increased amounts of creatinine present in the blood of these nephritic patients into methyl guanidine?

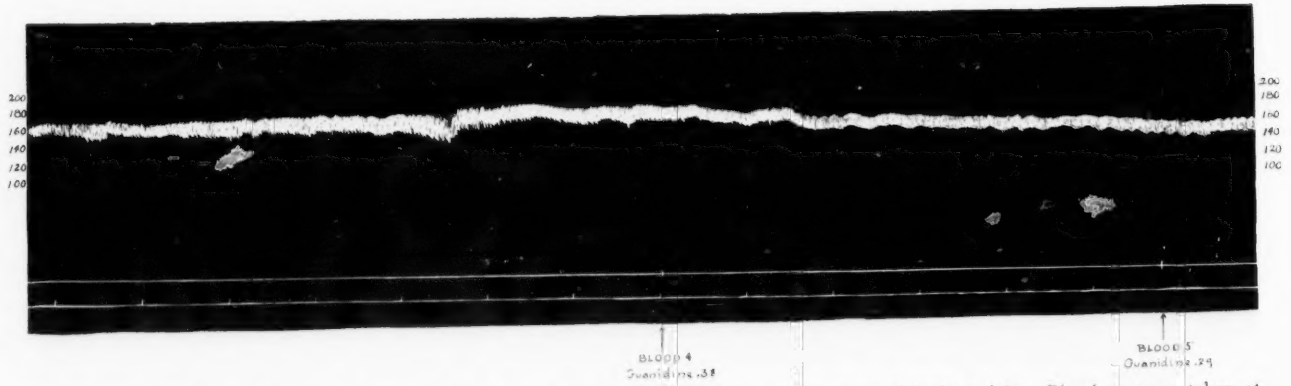

Fig. 1.—Dog injected with two doses each 10 mg. methyl guanidine sulphate per kilogram of body weight. Blood pressure taken at beginning of experiment was from 120 to 130 mm. The last injection was made five minutes before the portion of the curve shown. Note the continuous elevation of the blood pressure with blood guanidine varying from 0.29 to 0.38 mg. per hundred cubic centimeters.

We have studied the first question by observing the increases in the blood guanidine produced by the injection of sufficient amounts of methyl guanidine sulphate to elevate the blood pressure. These observations were made on six dogs and three of the curves are shown in figures 1, 2 and 3.

TABLE 2.—*Guanidine Readings in a Series of Patients with Arterial Hypertension* *

No.	Age	Blood Pressure	Protein Nitrogen	Creatinine	Creatine	Uric Acid	Guanidine Reading	Guanidine Corrected	Remarks
1	54	180/120	40.0	1.6	5.6	5.0	.57	.41	
2	50	156/110	35.7	1.3	4.9	3.1	.44	.27	
3	36	200/134	33.3	1.4	5.2	4.0	.44	.28	
4	74	176/110	30.0	1.3	4.6	3.3	.22	.13	Marked arteriosclerosis
5	70	192/130	37.0	1.3	3.1	4.1	.33	.16	Marked arteriosclerosis
6	40	176/110	37.5	2.0	4.5	5.4	.36	.09	Diabetes
7	48	190/112	35.0	1.5	4.8	4.1	.42	.13	Carcinoma of breast
8	72	175/110	29.0	1.4	3.8	2.4	.23	.04	Arteriosclerosis
9	51	194/130	86.0	3.6	5.1	5.3	.65	.39	
10	40	180/130	315.	12.0	5.6	5.3	1.1	.67	Chronic nephritis
..	..	170/120	183.	18.5	...	8.0	2.4	2.3	Chronic nephritis uremia
11	27	200/140	97.8	8.3	...	4.7	.49	.28	Chronic nephritis
..	..	200/140	89.0	11.	1.4	3.9	.67	.54	Chronic nephritis
..	..	180/130	77.0	8.7	6.7	5.0	.94	.45	Chronic nephritis
12	45	210/100	33.0	1.2	3.0	2.7	.38	.2	
13	47	180/120	30.0	1.1	2.9	...	.38	.21	
14	63	196/98	31.0	1.3	2.7	3.2	.33	.12	Aortic insufficiency
15	34	180/110	28.7	1.3	5.0	3.3	.4	.1	
16	44	185/120	28.0	1.2	3.8	3.6	.48	.25	
17	48	144/80	48.0	1.7	4.5	5.1	.6	.33	Hemiplegia cardiac failure
18	57	190/130	39.6	1.4	4.5	3.46	.34	.07	
19	30	160/120	37.0	3.	3.3	2.75	.38	.18	
20	57	178/124	37.5	2.4	3.	3.2	.43	.25	
21	65	180/120	33.0	1.3	4.2	6.1	.32	.26	
22	55	178/95	35.0	1.3	3.7	4.7	.32	.25	
23	66	214/130	36.5	1.1	3.2	...	.44	.28	
24	24	160/110	188.0	13.7	2.3	...	1.6	1.3	Chronic nephritis uremia
25	66	214/130	36.5	1.1	3.2	...	.44	.28	
..	..	220/134	33.0	1.3	...	...	.42	.3	
26	35	240/140	91.0	4.9	5.1	6.1	.46	.15	
..	..	.....	156.0	9.6	10.	9.4	1.2	.68	
27	42	190/120	92.0	4.3	3.5	...	.46	.25	
..	..	170/110	31.0	1.2	6.2	...	.56	.3	
28	47	180/120	40.0	1.9	...	...	.62	.48	
29	68	234/130	33.0	1.2	5.6	4.1	.55	.29	
30	32	255/145	30.0	1.5	4.3	3.6	.31	.14	
31	54	180/120	34.0	1.2	4.6	6.	.31	.19	
32	43	180/120	30.0	1.6	5.3	3.8	.27	.16	
33	42	170/110	31.0	1.5	5.1	4.9	.36	.17	
34	39	240/130	35.3	1.8	4.	4.9	.33	.22	
35	65	200/130	71.0	2.6	3.5	...	.33	.2	

* Blood chemistry in milligrams per hundred cubic centimeters of blood.

The curves show that a blood guanidine increase from 0.14 to 0.28 mg. per hundred cubic centimeters may be sufficient to produce a marked elevation in blood pressure. Such values are no higher than those obtained in many patients with arterial hypertension and suggest strongly that the increases noted in certain hypertensives, if they are really due to guanidine, are sufficient to produce an elevation in blood pressure.

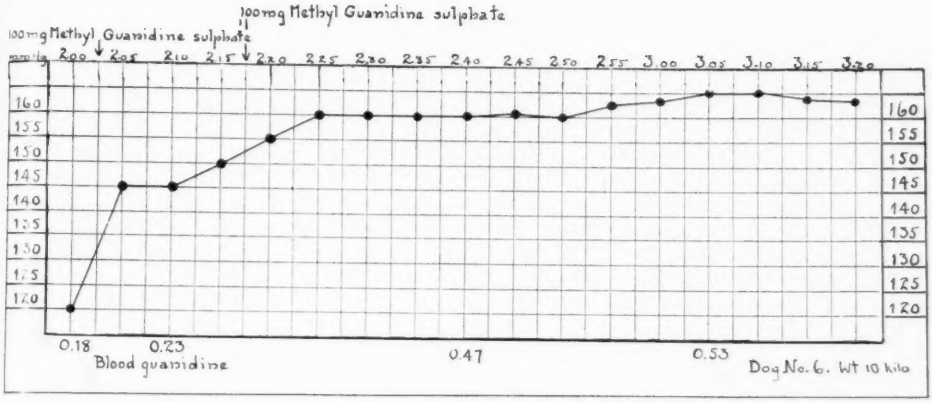

Fig. 2.—Curve drawn from complete tracing of an experiment. There was a marked elevation of blood pressure with only moderate increase in blood guanidine.

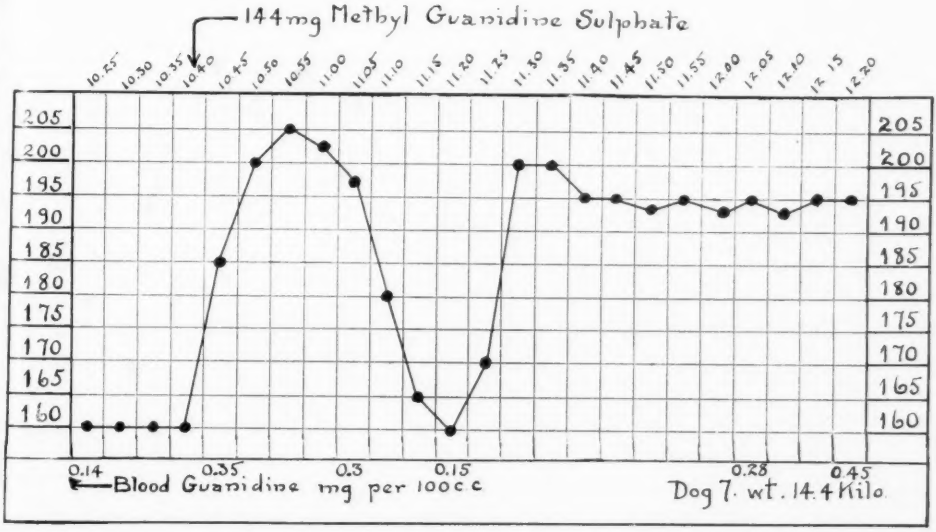

Fig. 3.—Observation similar to figure 2. Note the sudden fall in blood pressure, accompanied by a lowering in blood guanidine; then a subsequent rise. Such fluctuations are not uncommon. The explanation of them is not apparent.

The possible conversion of creatinine into methyl guanidine by the method with a resulting error in the patients having high blood creatinine, was studied in a series of experiments. In these experiments, definite amounts of creatinine (Eastman) were added to samples of blood which were then examined for guanidine by the method described in this article. The results are shown in table 3.

These observations show that the added creatinine does not produce change in the color reaction as compared with the control until the blood creatinine reaches the high value of 20 mg. per hundred cubic centimeters or more. The increase in the final blood "guanidine" value with 20 mg. of creatinine per hundred cubic centimeters is only 0.1 mg.; so

TABLE 3.—*Results of a Series of Experiments in Which Creatinine is Converted Into Methyl Guanidine*

Blood No. 1	Creatinine Added per Hundred Cubic Centimeters	Reading	Blood Guanidine (uncorrected)
Normal	.....	(1)	0.42
Normal	.....	(2)	0.44
Normal	5 mg.	(1)	0.42
Normal	5 mg.	(2)	0.42
Normal	10 mg.	(1)	0.44
Normal	15 mg.	(1)	0.44
Normal	25 mg.	(1)	0.5
Normal	35 mg.	(1)	0.54
Blood No. 2			
Normal	.....	(1)	0.38
Normal	.....	(2)	0.35
Normal	10 mg.	(1)	0.36
Normal	10 mg.	(2)	0.37
Normal	10 mg.	(3)	0.38
Normal	10 mg.	(4)	0.38
Normal	20 mg.	(1)	0.51
	.....	(2)	0.47
	.....	(3)	0.50

it seems impossible that the high guanidine values in patients 10, 11 and 24 were due to the increase in blood creatinine in these patients.

We have studied four patients with uremia, all of whom have shown high "guanidine" blood values. In one patient with uremia, not included in this series because of a difference in the method of determination, the high blood "guanidine" of 3 mg. per hundred cubic centimeters was seen.

In dogs, we have frequently seen convulsions after the injection of methyl guanidine sulphate when the blood showed 1 mg. guanidine per hundred cubic centimeters, or higher. This suggests that if the increase in the color reaction in the blood of these patients with uremia is actually due to guanidine, it may be present in amounts sufficient to produce toxic effects such as convulsions.

We realize that we do not have any proof that the color reaction in the blood is due to guanidine. The reaction is, however, given by

guanidine, which is a pressor substance. We have found increased amounts in fifty observations on patients suffering from arterial hypertension, including six cases of frank nephritis. The final proof that this color reaction is due to guanidine can only come with the isolation of guanidine from the blood, and if it is present only in the small amounts indicated by the colorimetric examination, such isolation will probably be extremely difficult.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

I. GROWTH FACTOR IN DEFECTIVE CALCIFICATION *

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AND
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It is our purpose to present in this paper the roentgenographic evidence of a high grade osteoporotic condition developing in the long bones of jaundiced puppies and to give further data on the blood calcium of these animals. The results obtained from a study of several litters enable us to present a more comprehensive report and to substantiate the observation made recently [1] that a fairly uniformly progressive calcium deficiency occurs during this early period of growth. Whereas progressive loss in weight and cachexia obtain for the jaundiced adult animal, the young one shows a progressive gain in weight which is appreciable at the time of death, although emaciation may have supervened. Investigators in this field have limited themselves entirely to a study of the adult animal, and extended work has not been carried out on the very young. It seemed advisable, therefore, to investigate further the disturbances which might be expected to arise in the growing young animal with its low storage of calcium.

METHODS

These experiments extended over a period of twelve months. Five litters, comprising twenty-four puppies from 8 to 10 weeks old, were used. The puppies in two litters were allowed to live their span of life after the induction of jaundice, and those in three litters were used for another set of experiments before the twentieth day of jaundice (thyroparathyroidectomized). Four control animals were kept. One of the animals on which operation was performed served as an excellent control in that it reestablished a bile flow to the intestine through regeneration of the bile passages. The common duct was divided between ligatures in nine animals; eleven in addition to this had their gallbladders removed.

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* Read before the American Physiological Society, Rochester, N. Y., April 14, 1927.

* From the Nelson Morris Fund and the John D. and Fannie K. Hertz Fund of the Michael Reese Hospital, the Nelson Morris Institute for Medical Research, and the Department of Physiology of the University of Chicago.

1. Buchbinder, W. C., and Kern, Ruth: Blood Calcium Deficiency in Experimental Obstructive Jaundice, Am. J. Physiol. **80**:273 (April) 1927.

The animals were allowed to run free in a room. They were taken outdoors almost daily for a short while, even during the winter months. Their diet consisted of various kinds of meat, raw and cooked, dog biscuits, cooked vegetables (including tomatoes) and cooked cereals. Orange juice was added to the diet. The animals were allowed a liberal quantity of milk (3 quarts to five animals). During transient periods of anorexia, milk constituted their chief diet. The animals were allowed to eat as much as they desired.

A record of the animals' weights was kept. Determinations of blood calcium were made at the beginning of the experiment and during the period of jaundice at intervals of from ten to twenty days. The Kramer-Tisdall [2] technic was used, and duplicate determinations were made, except in few instances. Roentgenograms of the front extremities of all animals were made at the beginning of the experiment. They were taken in three litters of the puppies from sixteen to eighteen days after the induction of jaundice; in two litters, between the sixtieth and seventieth day of jaundice.

Electrocardiograms were made of the animals of the latter group, and an accurate record was kept of the pulse rates. The results obtained from this part of the experiment will be published as a separate report.

RESULTS

An examination of the data given in tables 1 and 2 (charts 1 and 2) for nineteen jaundiced puppies after twenty days of induced jaundice did not reveal significant changes in the blood calcium level, although there was a suggestion of lowering. At this time the gain in body weight (nine animals) amounted to 16 per cent. The animals showed definite signs of impaired nutrition and were slightly less active than the normal controls. They acquired a distaste for certain foods, and at times their appetites were capricious. Generally it was equal to that of their nonjaundiced mates, and it was often voracious. Vomiting was rarely noted. The stools were clay colored, and often liquid and spotted with blood.

An increase in body weight was noted up to the sixtieth day, at that time amounting to 66 per cent (five animals). The percentage of decrease in the blood serum calcium was almost equal to that of the gain in body weight (56.6 per cent decrease in blood calcium for four animals). Not only was there a complete absence of neuromuscular irritability, but there was some degree of apathy. At this time, a greatly

2. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serum and Plasma, Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921.

increased growth of skeletal structures was noted (fig. 1). Between the seventy-fifth and one-hundredth day the animals did not fare so well and lost weight. Although marked emaciation may have supervened before death, their body weight was considerably above that at the time jaundice

TABLE 1.—*Calcium Determination for Calcium in Blood Serum of Jaundiced Puppies*

	Initial Calcium	Days After Induction of Jaundice										
		10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	100-110	120-130
Queenie	13.2	....	12.1	....	....	9.5	....	....	....	9.6	....	....
Gretchen	11.8	....	11.9	....	....	9.3, 8.7	....	....	....	....	....	....
Whitefoot *	11.6	....	12.0	....	11.1	....	....	10.9	....	11.9	....	....
Sandy *	12.9	....	12.3	....	10.9	....	....	11.5	....	11.8	....	....
Sarah *	10.2	....	8.0	....	7.0	†	6.7	....	10.8	10.3	....	....
Bimbo	10.5	10.4	....	8.0	....	....	....	....	....	....	....	....
Mike	10.2	9.9	8.8	....	....	7.0	5.1	....	....	5.0	7.0	6.2
Doc	13.2	....	11.8	Died during the second operation								
Mary	12.1	10.8	....	....	8.2	....	7.8	....	....	8.2	....	....
Bubbles	9.9	....	6.7	....	5.8	....	7.1, 5.4	....	....	....	....	....
Average	11.6	10.4	10.4	8.0	7.0	8.5	6.4	....	....	8.3	7.0	6.2

* Control animals.

† Jaundice clears up, urine free of bile pigment. Autopsy revealed reestablishment of bile flow to the intestine.

TABLE 2.—*Determinations for Calcium in Blood Serum of Puppies Jaundiced from Sixteen to Eighteen Days (Animals Were Then Thyroparathyroidectomized)*

	Initial Calcium	
Ann *	11.7	14.4
Cinder *	10.5	14.1
Tan	10.1	11.6
Wolf	10.2	11.1
Cinderella	9.9	9.5
Bob	8.5	8.5
Brownie	13.4	9.6
Spotty	11.8	10.3
Ulysses	12.0	9.7
Hermine	12.7	9.7
Tippy	12.4	10.1
Ear	11.6	11.3
Sacro	11.2	8.7
Averages	11.2 (13)	10.0 (11)

* Control animals.

was initiated. They finally showed signs of severe chronic intoxication. Alternating periods of ascites and hydremia with dehydration states were noted in two animals. This probably most readily accounts for the rise in the blood calcium in the last stages of jaundice (table 1, dogs 1 and 10). They also developed a relative tachycardia with

inversion of the T-wave of the electrocardiogram. In this respect, the effects of prolonged obstructive jaundice appear to be cumulative.

Roentgenographic studies made on three litters in which the animals were jaundiced for twenty days did not reveal any changes in bone density or structure; they were altogether like those of the controls. Roentgenograms taken from sixty to seventy days after the induction

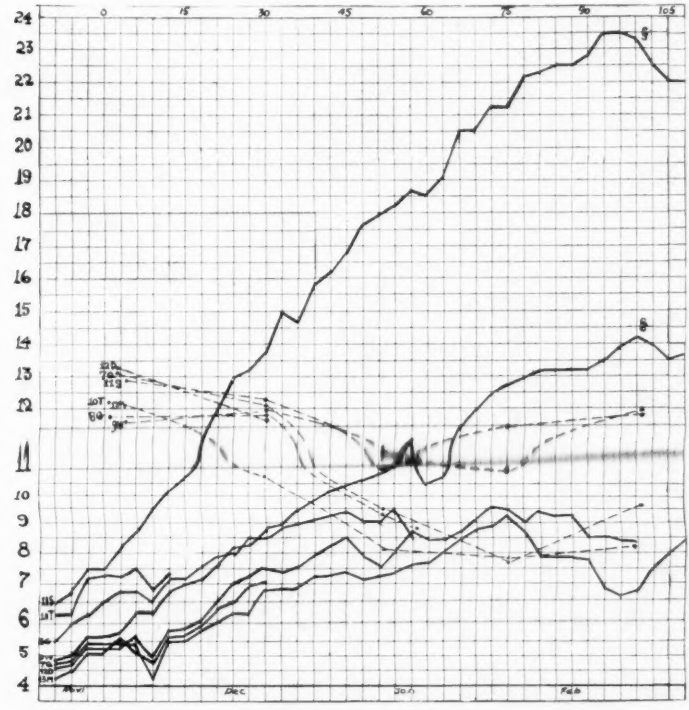

Chart 1.—Decrease in blood serum calcium with an increase in body weight in a litter of animals. The broken line indicates the calcium, and the unbroken line the weight. Numbers 11 S and 9 W show the curves for the control dogs. The § indicates the division of the common duct in control dogs. The ordinates represent milligrams of calcium per one hundred cubic centimeters of blood and pounds of body weight. Each division of the abscissa represents three days.

of jaundice disclosed a high grade rarefaction, cortical thinning with relatively wide medullary spaces and a lack of contrast generally. This is best shown by a comparison of the metatarsal bones of the jaundiced animals with those of the controls (figs. 2, 3, 4 and 5).

REVIEW OF LITERATURE

Since the first quantitative studies of the calcium balance in obstructive jaundice by King, Bigelow and Pearce were published,[3] a number of reports have appeared on the blood calcium in jaundice. Although numerous methods have been employed, results obtained point almost uniformly to constant and normal calcium values. Snell, Greene and Rowntree[4] found a practically constant and normal calcium value, and Snell,[5] using the Kramer-Tisdall technic, found that the blood calcium remains well within the normal range in many jaundiced patients and

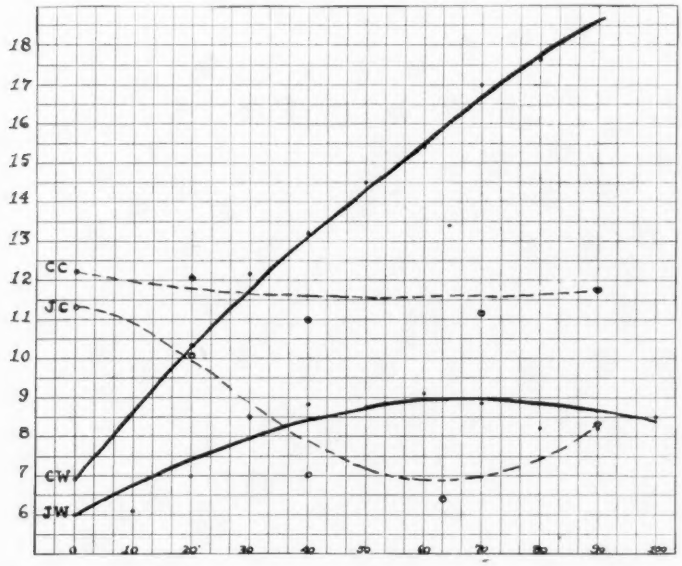

Chart 2.—Composite graph of the calcium and body weight curves. The ordinates represent pounds in body weight and milligrams of calcium per one hundred cubic centimeters of blood. The hollow circle and broken line indicate the calcium. The curve marked C. C. shows the calcium for the control dogs and that marked J. C., the calcium for the jaundiced dogs. The solid circle and unbroken line indicate the body weight (for only two animals). The abscissas represent days after the induction of jaundice.

3. King, J. H.; Bigelow, J. E., and Pearce, L.: Experimental Obstructive Jaundice, J. Exper. Med. **14**:159 (Aug.) 1911.

4. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med. **36**:273 (Aug.) 1925.

5. Snell, A. M.: Personal communication.

Fig. 1.—Growth of skeletal structures is evident in the dogs at either end of the group that were jaundiced seventy-five days. Both dogs have marked ascites. The animal in the center is a control. The three are litter mates. Roentgenogram of the dog in the left is seen in figure 4.

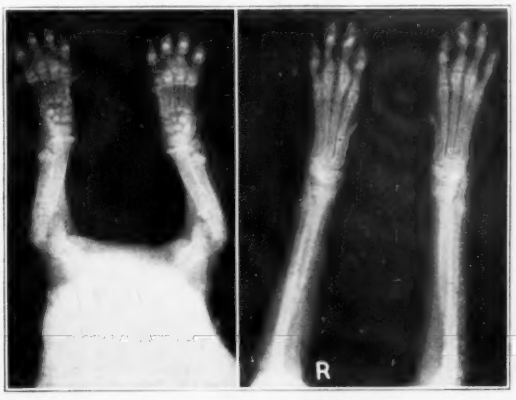

Fig. 2.—Normal physiologic depositions of lime salts the result of growth.

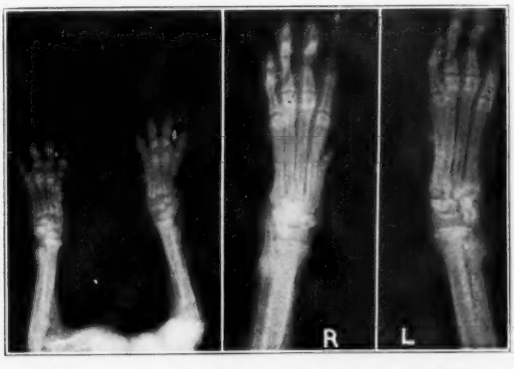

Fig. 3.—Normal physiologic depositions of lime salts the result of growth.

animals. The observations of Koechig,[6] Halvorson, Mohler and Bergheim,[7] who used other methods for determinations for calcium, are in agreement with the foregoing.

The quantitative studies of King, Bigelow and Pearce disclosed a loss of calcium from certain of the tissues, notably bone and heart, and an increase in the calcium of the blood. The bone of the jaundiced dog

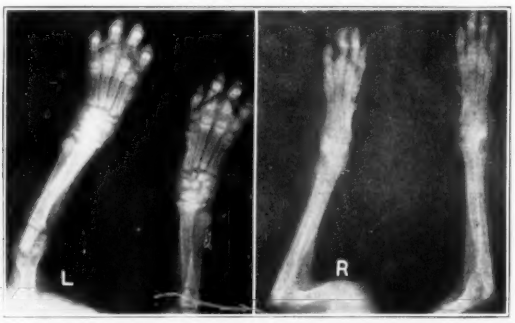

Fig. 4.—Roentgenograms of the prejaundiced state and that sixty days after the induction of jaundice. A comparison of the metatarsals of these animals and those shown in figures 2 and 3 reveals a distinct thinning of the cortex, relatively wide medullary spaces and a lack of film contrast.

Fig. 5.—The same conditions are illustrated here as in figure 4.

showed a striking loss, which pointed to this organ as furnishing most of the calcium to combat an intoxication. Hypercalcemia in jaundice has not been noted by subsequent investigators, nor have we been able to

6. Koechig, I.: The Calcium Control of the Blood in Pathologic Conditions, J. Lab. & Clin. Med. **9**:679 (July) 1923.

7. Halvorson, J. O.; Mohler, H. K., and Bergeim, O.: The Calcium Content of the Blood Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171 (Nov.) 1917.

find any reference to other quantitative studies applied to skeletal structures in this state. Their finding of a loss of calcium in the heart throws some doubt on the accuracy of their entire work since, in his researches, Collip [8] disclosed a special affinity of this organ for calcium in hypercalcemic states following the use of his extract.

The pioneer work of Rohrig [9] in investigating the cardiovascular effects of bile resulted in the conclusion that bile owes its toxicity to the bile salts. Most investigators have been of this opinion.[10] King and Stewart [11] presented evidence that the toxicity of bile is due to the pigment, and afforded some evidence as to how calcium may serve the organism in a physiologic and protective fashion. They showed that the lethal dose of uncombined pigment corresponded almost exactly to the amount of pigment in the lethal dose of whole bile, and that when a prepared calcium biliverdinate was injected into the circulation, toxic effects were absent. More recently, Walters and Bowler,[12] studying the rate of excretion of calcium chloride in the jaundiced and normal animal, showed a marked avidity of the former for calcium. It required about two times the amount of injected calcium to raise the blood calcium level of the jaundiced animal to the same level as that of the normal one in spite of the fact that the blood calcium content was practically the same in the jaundiced and normal animals before and after the injection of a lethal dose. This suggested to these authors a calcium deficiency that was not apparent.

COMMENT

The nutritional state of our animals varied at the beginning of the experiment, and it was common to note rachitic changes. Some of the animals developed cretinoid characters (fig. 6), but an increase in the length of long bones was always observed. The roentgenograms revealed this in all instances. Growth potentialities of animals of mixed breeding even though of the same litter are factors that have to be reckoned with, especially in designating controls. There is, however, a constant striking contrast in the calcification processes of what we

8. Collip, J. B.: Harvey Lectures, Baltimore, Williams & Wilkins Company, 1925-1926, p. 142.

9. Rohrig, A.: Arch. d. Heilkunde, **4**:385, 1863.

10. Since the manuscript was completed, Horrall has reported his conclusion that the only toxic agents in bile are the salts of the bile acids. (Horrall, O. H.: Toxicity of Bile, Am. J. Physiol. **81**:486 [July] 1927.)

11. King, J. H., and Stewart, H.: Effect of the Injection of Bile on the Circulation, J. Exper. Med. **11**:673 (Sept.) 1909.

12. Walters, W., and Bowler, J. P.: The Preoperative Preparation of Patients with Obstructive Jaundice: An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, Surg. Gynec. Obst. **39**:200 (July) 1924.

have assumed to be normal physiologic growth and those occurring in the jaundiced animals of the same litter. Quantitative methods need to be applied to determine whether the changes in bone are the result of lysis, i. e., the removal of calcium from bone already formed, or of actual but deficient deposition of lime salts into an increased matrix.

We have enumerated the chief intrinsic factors operating in the production of the faulty calcification as follows (they are concurrent, and it is difficult without quantitative data to evaluate them): First, the total body calcium in the animals used in the experiment is small. Sherman and MacLeod [13] have shown that in mice there is an increase in the percentage of body calcium from 0.25 to 0.6 per cent after the first fifteen days of existence. A correspondingly longer interval for

Fig. 6.—Animal jaundiced 100 days. Note the cretenoid characters. This animal developed bilateral bone cysts (fig. 5).

such an increase could be expected in the dog. Second, a grave metabolic disorder is present; osteoblastic tissues should have an extremely unfavorable environment in which to build bone. Third, there is an intestinal factor, the effect of the exclusion of bile from the intestine apart from the serious digestive disturbances that arise. Finally, there is a growth factor; new bone production exceeds the rapidity with which lime salts are deposited.

The normal blood calciums that obtain in the adult animal throughout the course of obstructive jaundice when the same serious digestive disturbances arise would speak against any great defect in the capacity of the intestine to absorb calcium. In the young animal that has been jaundiced twenty days, significant changes in the blood calcium level

13. Sherman, H. C., and MacLeod, F. L.: The Calcium Content of the Body in Relation to Age Growth and Food, J. Biol. Chem. **64**:429 (June) 1925.

are not noted. If changes in the skeletal structures of the adult animal occur in late obstructive jaundice, such observations have escaped clinical recognition. On the other hand, the severe osteoporosis that develops in the animal with a persisting fistula of the biliary tract is well established. Pawlow [14] and his co-workers noted this, and more recently Whipple [15] called attention to the thinning of the bone, the loss of inorganic salts and a tendency to spontaneous fracture in this condition. Osteoporosis has also been observed in man [16] with fistulas of the gallbladder. Total exclusion of bile from the intestine is the only thing obviously in common in the two gross disturbances of the biliary tract; in obstructive jaundice, a retention of the biliary constituents in the blood and tissues follows. Such evidence would tend to support the idea that a close relationship exists between the extrahepatic functions of bile and the metabolism of bone. In the young animal, in which anabolic processes predominate, perhaps the loss of vitamins, antirachitic factors, and possibly the absence of some catalytic agent normally present in bile, may also play important rôles in the production of faulty calcification.

A slight lowering of the calcium in the blood serum is to be noted thirty days after the induction of jaundice. At this time the roentgenogram does not reveal significant changes in the density of bone structure, although quantitative studies might disclose such changes. The high degree of rarefaction parallels the marked lowering of the blood calcium after from forty to fifty days of induced jaundice. It might therefore be argued that here, as in other states of calcium drain, the structural changes are secondary. The belief that some rôle of the parathyroids in maintaining free from tetany those animals with low calcium values, the animals exhibiting not the slightest neuromuscular irritability but actually some degree of apathy, would further support the notion that such a mobilization had occurred. Calcium values in the blood might still remain low as a result of either increased excretion or some precipitating mechanism already mentioned. The progressiveness of the calcium deficiency also calls for an explanation, even though we are in the realm of speculation. Sendroy and Hastings [17] concluded that "we are

14. Pawlow: Im Laboratorium gemachte Beobachtungen über die Knochenforshungbeim Hunde, Verhandl. d. gesellsch. Russ. Aerzte zu St. Petersburg **72**:314, 1904.

15. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, Physiol. Rev. **2**:440 (July) 1922.

16. Seidel, H.: Permanente Gellenfistel und Osteoporose beim Menschen, München med. Wchnschr. **39**:2034, 1910.

17. Sendroy, J., Jr., and Hastings, A. B.: Studies of the Solubility of Calcium Salts: III. The Solubility of Calcium Carbonate and Tertiary Calcium Phosphate under Various Conditions, J. Biol. Chem. **71**:797 (Feb.) 1927.

dealing with a complex system adjusted to function under normal conditions in such a manner as to furnish the organism with the optimum quantity of calcium wherever and whenever it is needed." In the main, the underlying mechanisms for the causation of the blood calcium deficiency and defective calcification seems to be closely related to growth and nutrition, and both are progressive from the time of the induction of jaundice. If there is a relative curtailment of calcium assimilation necessary for growth processes early in the period of jaundice, it is reasonable to assume that the organism is drawing on its resources in the bones, even though their endowment is small. It would be difficult to establish a sudden breaking point for absorption of calcium late in the period of jaundice on the basis of pathologic-anatomic grounds. The progressive lowering of calcium in the blood serum occurring at a time of marked growth of the bones is highly suggestive. We would, therefore, suggest that uncalcified bone is formed as the result of the production of new bone at a rate which exceeds the rapidity with which calcium phosphate is deposited, but that there occurs an actual but deficient deposition of lime salts into this increased bone matrix.

SUMMARY AND CONCLUSIONS

A fairly uniformly progressive calcium deficiency occurs in the blood serum of jaundiced puppies during the period of growth.

The progressive lowering of the blood calcium is attributed to the deposition of lime salts into an increased matrix rather than to a breaking point in the intestine resulting in progressive failure of calcium absorption.

The maintenance of normal calcium values in the early stages of jaundice may be due to mobilization, namely, bone lysis.

The roentgenograms disclose a marked degree of rarefaction sixty days after the induction of jaundice. This is manifested by cortical thinning, relatively wide medullary spaces and a lack of contrast generally. After twenty days of jaundice, significant changes in bone density or structure do not occur. One animal developed bilateral cysts in the bones.

The four intrinsic factors in the production of faulty calcification are: small calcium storage; the presence of a disturbed metabolic condition unfavorable to osteogenesis; an intestinal factor in which the absence of some catalytic agent in bile may be most important, and production of bone which exceeds the rapidity with which lime salts are deposited.

The observations made in these experiments, together with such other evidence as we have, lend support to the idea that the extrahepatic functions of bile are closely related to normal bone metabolism.

Book Reviews

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOL. XI, SURGERY, PART 1, GENERAL SURGERY, ORTHOPEDIC SURGERY, NEURO-SURGERY. Pp. 1,300 with 600 illustrations. Washington, D. C.: Government Printing Office, 1927.

This volume is beautifully bound and printed, and the illustrations are lavishly scattered through the pages.

As a historical work the book will be of great value. While containing little that is original, every phase of war surgery is covered by a real expert, usually the one whose special studies form the basis of the present views. Most of the material is slightly rewritten from former scattered publications, but it is well reorganized into a carefully knit unit and forms a clear record of the war experiences of a number of scientists.

After two chapters on the material of war, effect of gunfire, etc., an enormous section on statistics follows, which is remarkable for its completeness. Every war injury is tabulated and classified and page after page of tables show the mortality and morbidity and other details of various types of wounds and fractures.

In the section on general surgery special praise is due to Yates for the clear and concise summary of the newer knowledge of dealing with wounds of the chest. Much clinical and experimental work is cited, and this new field in surgery is thoroughly covered. The lessening of the mortality from such wounds following the introduction of modern methods is striking.

De Tarnowsky's article on "Surgery at the Front" is also of great worth and could well serve as a guide in some future war to organize a medical service from the trenches to the base hospital.

The section on orthopedic surgery is adequate but not of great interest on account of the fact that the war brought about but few changes in this type of work. The mechanical aids to surgery, however, are well described and their use explained.

Part 3, neurosurgery, is thorough and contains articles of Cushing, Frazer, Pollock and others. In this field many additions to our knowledge were gained by intensive study and the section is therefore of great interest.

The final chapter by Huber dealing with his experimental work on nerve regeneration is worthy of highest praise, as is the work of Pollock on peripheral injuries.

A great section of the volume is taken up by the studies on wound shock and the methods of combating wound shock. This work was largely done in collaboration with a number of physiologists. Much of the experimental work was done hastily under the stress of active warfare and is perhaps rather inconclusive. However, it is the vast experience of a great many surgeons as well catalogued in a symposium on this matter and it cannot fail to be of great value to further military surgeons. Indeed, the whole book seems to be more of a history than a scientific contribution, and in this field it is doubtful if the object could have been any better achieved.

TRABAJOS Y PUBLICACIONES — DE LA CLINICIA. By PROFESSOR PEDRO ESCUDERO. Price, $12. Buenos Aires: El Ateneo, 1925.

This is the fourth volume of the collected publications of the Escudero Clinics, and serves to call attention to the enormous amount of high class scientific work being contributed in the schools of our sister republic.

The work opens with a detailed report covering about 150 pages of eight cases of Ayerzas' disease, the syndrome given rise to by sclerosis of the pulmonary arteries. The thoroughness and completeness with which these cases of "black cardiacs" were studied is commendable. Every means known

to medical science was applied and the syndrome can now be stated to have been placed on a firm basis so that diagnosis should be made in every case. While many of the articles in the book are of this type, i. e., meticulously and carefully detailed case reports, they compare favorably with any that I have ever seen.

The article on hyperglycemia and that on gerodermia may be placed in this category.

Escudero himself, in a short report, presents a very interesting and new conception of the pathogenesis of Banti's disease. He believes that the primary lesion is a chronic perispleenitis. This perispleenitis by itself mechanically gives rise to aplastic anemia with leukemia and a mild nucleosis, and the enlargement of the spleen in turn brings about a hepatic sclerosis, thus completing the picture of Banti's disease. He has observed cases illustrating each stage of this condition and is rather convinced that syphilis is an element in its etiology. A good deal of the work is of a negative nature, but nevertheless is important.

A parental administration of casein is shown by Peco to have no effect on the hyperglycemia of diabetes.

Puchulu shows that the administration of insulin has little, if any, effect on the course of hyperthyroidism, and Izzo also shows that insulin has no effect on the course of tuberculosis of the lung, and that the treatment of tuberculous diabetes by insulin has no effect on tuberculosis.

The volume is lavishly illustrated with photographs, roentgenograms, electrocardiagraphs and other charts, and represents indeed a monumental work to be produced in one year.

MANUAL OF MATERIA MEDICA FOR MEDICAL STUDENTS. By E. Q. THORNTON. Price, $4.50. Pp. 384. Philadelphia: Lea & Febiger, 1927.

This book of 384 pages is essentially a catalogue of drugs listed in the U. S. Pharmacopeia with a brief statement of origin and general character of the drugs. It is essentially an enlarged model of *Useful Drugs* (A. M. A.) and, as stated in the preface, does not attempt to present to the medical student a pharmacologic basis underlying clinical usage of the drugs. Such a book as this appears to be entirely uncalled for and would seem to have no place in the teaching of modern pharmacology and therapeutics to medical students.

OVERCOMING TUBERCULOSIS: AN ALMANAC OF RECOVERY. By GERALD B. WEBB, M.D., and CHARLES T. RYDER, M.D., Colorado School of Tuberculosis, Colarado Springs, Colo. Third edition, revised. Cloth. Price, $2. Pp. 81, charts additional. New York: Paul B. Hoeber, Inc., 1927.

This is the third edition of the former work "Recovery Record; for Use in Tuberculosis," by the same authors. The title has been changed and certain minor changes and additions have been made. It is a valuable compendium for the tuberculous patient, and sufficient charts are appended to allow a daily record to be kept for over two years.

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